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BioNeutra™

BioNeutra Inc.

Transforming Natural Products into Better Health

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March 17, 2008

Robert L. Martin
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD
U.S.A. 20740-3835

RE: GRAS NOTICE FOR VITASUGAR™, AN ISOMALTO-OLIGOSACCHARIDE (IMO) MIXTURE, FOR USE IN FOODS

Dear Dr. Martin:

In accordance with proposed 21 CFR §170.36 [Notice of a claim for exemption based on a Generally Recognized as Safe (GRAS) determination] published in the *Federal Register* [62 FR 18938 (17 April 1997)], I am submitting three (3) copies, as the notifier [BioNeutra Inc.; 9419-20th Avenue; Edmonton, Alberta, Canada], a Notice of the determination, on the basis of scientific procedures, that Vitasugar™, an isomalto-oligosaccharide mixture as defined in the enclosed documents, is GRAS under specific conditions of use as a food ingredient, and therefore, is exempt from the premarket approval requirements of the *Federal, Food, Drug and Cosmetic Act*. Information setting forth the basis for the GRAS determination, which includes a comprehensive summary of the data available and reviewed by an independent panel of experts (the Expert Panel) in support of the safety of Vitasugar™ under the intended conditions of use, as well as *curricula vitae* evidencing the qualifications of the members of the Expert Panel for evaluating the safety of food ingredients, also is enclosed for review by the agency.

I trust that the enclosed Notice is acceptable. Should you have any questions or concerns regarding this GRAS Notice, please do not hesitate to contact me at any point during the review process so that we may provide a response in a timely manner. I look forward to receiving acknowledgement of receipt of this notice.

Sincerely,

Dr. Jianhua Zhu
President/CEO

Encl.

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BY:----------

I. GRAS Exemption Claim

A. Claim of Exemption from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997)]

Vitasugar™ (powder and syrup), an isomalto-oligosaccharide (IMO) product as defined in the report in Appendix I entitled, "**EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF VITASUGAR™, AN ISOMALTO-OLIGOSACCHARIDE (IMO) MIXTURE, FOR USE IN FOODS**", dated March 12, 2007, has been determined by BioNeutra Inc. (hereafter BioNeutra) to be Generally Recognized as Safe (GRAS), consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*. This determination is based on scientific procedures as described in the following sections, under the conditions of its intended use in food, among experts qualified by scientific training and expertise. Therefore, the use of Vitasugar™ in food as described below is exempt from the requirement of premarket approval.

Signed,

March 17, 2008

Date

Dr. Jianhua Zhu, President
BioNeutra Inc.
9419-20th Avenue
Edmonton, Alberta, Canada
T6N 1E5
Tel: 1-780-466-1481
Email jzhu@bioneutra.ca

B. Name and Address of Notifier

Dr. Jianhua Zhu, President
BioNeutra Inc.
9419-20th Avenue
Edmonton, Alberta, Canada
T6N 1E5

Tel: 1-780-466-1481
Email: jzhu@bioneutra.ca

C. Common Name of the Notified Substance

Isomalto-oligosaccharides (Vitasugar™)

D. Conditions of Intended Use in Food

BioNeutra intends to market Vitasugar™ (syrup and powder) as a food ingredient in the United States for use as an alternative sweetener in conventional foods. The individual proposed food-uses and use-levels of Vitasugar™ are summarized in Table 1.

Table 1 Summary of the Individual Proposed Food-Uses, Use-Levels, and Amount per Serving of Vitasugar™ in the United States (U.S.)

Food-Uses	Serving Size (grams)[1]	Maximum Use-Level (%)	Vitasugar™ Amount per Serving (grams)
Baked Goods and Baking Mixes	60	25	15
Beverages and Beverage Bases	240	5	12
Breakfast Cereals	50	20	10
Condiments and Relishes	23	20	5
Dairy Product Analogs	240	5	12
Mayonnaise and Mayonnaise-type Dressings	23	30	7
Salad Dressings	30	30	9
Frozen Dairy Desserts and Mixes	100	10	10
Gelatins, Puddings, and Fillings	100	15	15
Gravies and Sauces	70	20	14
Hard Candies	10	100	10
Jams and Jellies	15	75	11
Meal Replacement Bars and Mixes	40	25	10
Meat Products	50	5	2.5
Milk and Milk Products	110	5	5.5
Nut Products	30	10	3
Processed Fruits and Fruit Juices	140	5	7
Snack Foods	30	5	1.5
Soft Candy	35	40	14
Sugar Substitutes	4	100	4
Sweet Sauces, Toppings, and Syrups	30	50	15
Processed Vegetables and Vegetable Juices	100	15	15

[1] Based on the Reference Amounts Customarily Consumed (RACC) Per Eating Occasion (21 CFR §101.12) (U.S. FDA, 2007a).

Based on actual projected production of Vitasugar™ of 16,000 tons by 2010, a *per capita* intake of approximately 0.2 g/person/day was estimated. Intake estimates also were determined based on the replacement of 2 servings per day of sucrose-containing foods with foods to which Vitasugar™ has been added. Assuming daily consumption of 2 servings of food which contain the highest amounts of Vitasugar™ per serving as indicated in Table 1 (*i.e.*, 15 g/serving), an intake exposure of not more than 30 g/person/day was estimated.

E. Basis for the GRAS Determination

Pursuant to 21 CFR §170.35, Vitasugar™ has been determined by BioNeutra to be GRAS on the basis of scientific procedures (U.S. FDA, 2007b). This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of Vitasugar™ as a component of food. The safety of Vitasugar™ is based on data generally available in the public domain on related isomalto-oligosaccharide ingredients, as discussed herein and in the accompanying documents [see Appendix I, "**EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF VITASUGAR™, AN ISOMALTO-OLIGOSACCHARIDE (IMO) MIXTURE, FOR USE IN FOODS**"].

F. Availability of Information

The data and information that serve as the basis for this GRAS Notification will be sent to the U.S. Food and Drug Administration (FDA) upon request, or will be available for review and copying at reasonable times at the offices of:

Dr. Jianhua Zhu, President
BioNeutra Inc.
9419-20th Avenue
Edmonton, Alberta, Canada
T6N 1E5

Tel: 1-780-466-1481
Email: jzhu@bioneutra.ca

Should the FDA have any questions or additional information requests regarding this notification, BioNeutra will supply these data and information.

II. Detailed Information about the Identity of the Substance

A. Identity

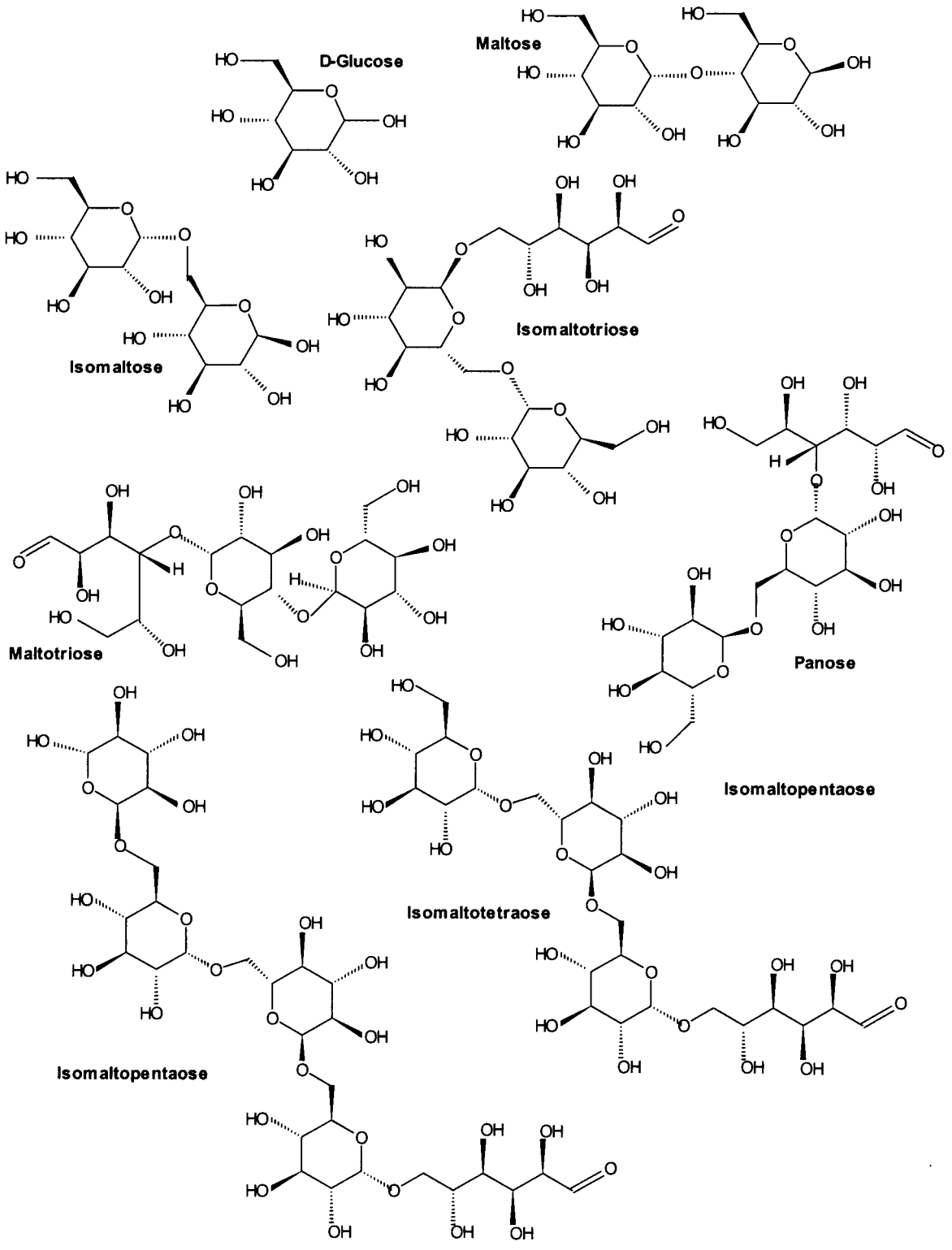
The syrup and powder Vitasugar™ products display a light-sweet taste. While the syrup is a pale yellow or colorless transparent liquid of a sticky consistency, the powder appears white in color.

The term "isomalto-oligosaccharide" typically defines glucose oligomers with α-D-(1,6)-linkages, including among others isomaltose, panose, isomaltotetraose, isomaltopentaose, nigerose, kojibiose, and higher branched oligosaccharides (PDRNS, 2001). The term oligosaccharide is used to describe a carbohydrate that is larger than a simple di- or trisaccharide, but smaller than a polysaccharide (greater than 6 units). The majority of oligosaccharides found in BioNeutra's

IMO products consist of 3 to 6 monosaccharide units linked together; however, disaccharides, as well as longer polysaccharides (up to 9 units) also are present. The disaccharide fraction of the IMO product consists of the α-1→4 linked maltose and the α-1→6 linked isomaltose, while maltotriose, panose, and isomaltotriose make up the trisaccharide fraction. The oligomers found in the IMO product include isomaltotetraose, isomaltopentaose, isomaltohexaose, isomaltoheptaose, and small amounts of oligomers with 8 or more degrees of polymerization. The exact distribution of the individual di-, tri-, and larger oligosaccharides in the IMO products is expected to vary depending on the manufacturing conditions used to produce the mixture.

Compositional analysis of sample lots revealed that the syrup and powder formulations contain between 15 and 20% of smaller saccharides (fewer than 3 glucose units). Oligosaccharides (3 to 6 degrees of polymerization) comprise approximately 77 and 73% of the syrup and powder composition, respectively. Oligomers (7 or more glucose units) account for not more than 10% the oligosaccharide composition. The structural formulas of saccharides at the lower end of the degree of polymerization range are presented in Figure 1.

Figure 1 **Structural Formulas of the Mono-, Di-, and Oligosaccharides (DP3 to DP5) Identified in BioNeutra's Isomalto-Oligosaccharide (IMO) Products (Vitasugar™)**



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The chemical names, CAS numbers, and empirical formulas of some of the lower weight saccharides identified in the IMO products are presented in Table 2.

Table 2 Chemical Description of the Saccharides in BioNeutra's Isomalto-Oligosaccharide (IMO) Products (Vitasugar™)

Common Name:	CAS No.:	Empirical Formula:	Chemical Name:
Monosaccharides (DP1)			
Glucose	50-99-7	$C_6H_{12}O_6$	D-Glucose
Disaccharides (DP2)			
Maltose	69-79-4	$C_{12}H_{22}O_{11}$	4-O-α-D-glucopyranosyl-D-glucose
Isomaltose	499-40-1	$C_{12}H_{22}O_{11}$	6-O-α-D-glucopyranosyl-D-glucose
Trisaccharides (DP3)			
Maltotriose	1109-28-0	$C_{18}H_{32}O_{16}$	O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-D-glucose
Panose	33401-87-5	$C_{18}H_{32}O_{16}$	O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,4)-D-glucose
Isomaltotriose	3371-50-4	$C_{18}H_{32}O_{16}$	O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-D-glucose
Oligo- and polysaccharides (DP4 to DP9)			
Isomaltotetraose (DP4)	35997-20-7	$C_{24}H_{42}O_{21}$	O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-D-glucose
Isomaltopentaose (DP5)	6082-32-2	$C_{30}H_{52}O_{26}$	O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-D-glucose
Isomaltohexaose (DP6)	6175-02-6	$C_{36}H_{62}O_{31}$	O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1-6)-D-glucose
Isomaltoheptaose (DP7)	6513-12-8	$C_{42}H_{72}O_{36}$	O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-D-glucose
Isomaltooctaose (DP8)	NA	$C_{48}H_{82}O_{41}$	O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-gucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-D-glucose
Isomaltononaose (DP9)	NA	$C_{54}H_{92}O_{46}$	O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-D-glucose

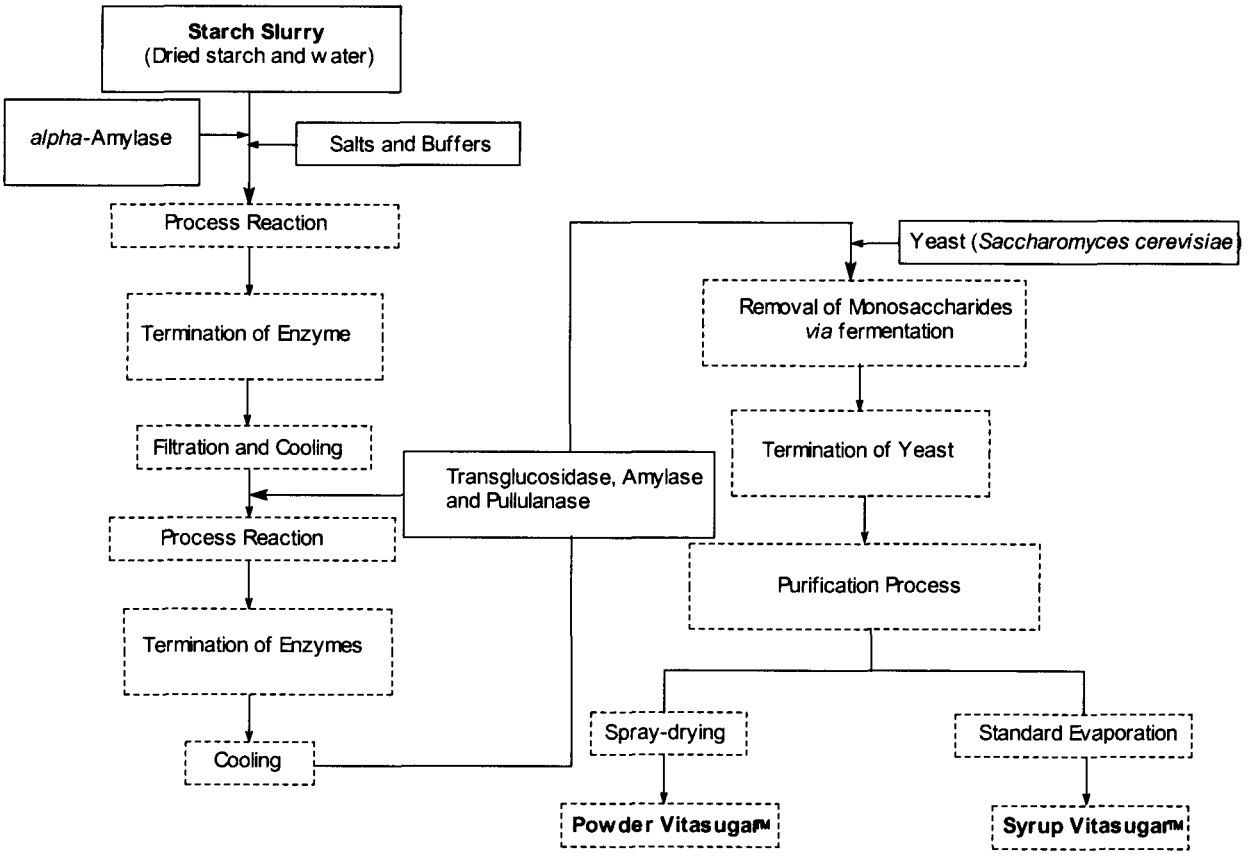
DP = Degree of polymerization; NA = Not available.

B. Method of Manufacture

Vitasugar™ is produced in accordance with current Good Manufacturing Practices (cGMP) *via* enzyme-catalyzed hydrolysis of starch raw materials (*e.g.*, corn, wheat, rice, cassava, barley, oats, potato, pulses *etc.*). A starting starch slurry (starch and water) is prepared to which α-amylases of fungal and bacterial origin (*Aspergillus oryzae* and *Bacillus licheniformis*, respectively), and a pullulanase from *Bacillus acidopullulyticus* are added to progressively

breakdown the amylose and amylopectin polysaccharides that make up the starch. An α-glucosidase from *A. niger* (transglucosidase L "Amano") is used to form the α-1→6 linkages comprising the isomalto units. Yeast is added to remove glucose that may form as a result of the enzymatic hydrolysis reactions. The temperature of the reaction mixture is increased to at least 90°C to terminate the enzymatic activity, which also ensures removal (by evaporation) of the alcohol (ethanol) that forms as a by-product of the yeast fermentation. Several down-stream purification steps are employed in the manufacturing of Vitasugar™ to minimize the potential for the occurrence of any residues of the biocatalysts or other processing aids used during the production process in the final products. All starting materials, processing chemicals, yeast, and enzymes involved in the manufacturing process are appropriate for food use. A schematic overview of the manufacturing process of Vitasugar™ is provided in Figure 2.

Figure 2 Schematic Overview of the Manufacturing Process for Vitasugar™



C. Specifications for Food Grade Material

The chemical, physical, and microbiological specifications for Vitasugar™ (syrup and powder) are presented in Table 3. Analysis of nonconsecutive representative lots demonstrated compliance with final product chemical, physical, and microbiological specifications. While ethanol that may have formed during the manufacturing process will be removed by evaporation as the temperature of the reaction mixture is increased to terminate enzymatic activity, several lots of the final product were analyzed for residual ethanol content. No detectable levels of ethanol (limits of quantification – 5 ppm) were identified in any of the sampled lots.

Vitasugar™ is expected to be as stable as other similar already marketed commercial monosaccharide/oligosaccharide sweetener products. Microbial growth is largely prevented as a result of the low moisture content of the product. In case that the product was to undergo degradation, progressively smaller saccharides and glucose units would be expected to form; however, study results have demonstrated that Vitasugar™ remains stable following storage for up to 14 weeks at pH 2 (room temperature).

Table 3 Physical, Chemical, and Microbiological Specifications for Vitasugar™ (IMO-syrup and IMO-powder)

Specification Parameter	Specification		Analytical Methods
	Syrup	Powder	
Solubility (water) (%)	N/A	≥99	-
Dried solids (g/100 g)	≥75	N/A	-
Glucose (% dry basis)	≤5[1]	≤5[1]	HPLC analysis
Isomaltose + DP3 to DP9 (% dry basis)	≥90[1]	≥90[1]	HPLC analysis
Moisture (%)	N/A	≤4	AOAC Method 925.45 (AOAC, 2000)[2]
pH	4 to 6	N/A	-
Sulfated ash (g/100 g)	≤0.3	≤0.3	<281> Residue on Ignition (USP, 2005)[3]
Heavy Metals			
Lead (mg/kg)	≤0.5	≤0.5	<251> Lead (USP, 2005)[3]
Arsenic (mg/kg)	≤0.5	≤0.5	<211> Arsenic (USP, 2005)[3]

Table 3	Physical, Chemical, and Microbiological Specifications for Vitasugar™ (IMO-syrup and IMO-powder)		
	Specification		
Microbiological Specifications			
Total Aerobic Plate Count (CFU/g)	< 10,000	< 10,000	MFHPB-18
Yeast	< 100	< 100	MFHPB-22
Escherichia coli (MPN/g)	< 10	< 10	MFLB-80 and MFLB-90
Salmonella (CFU/g)	Absent	Absent	MFHPB-20

N/A = Not applicable; DP = Degree of polymerization; HPLC = High Performance Liquid Chromatography; AOAC = American Organization of Analytical Chemists; USP = U.S. Pharmacopeia; CFU = Colony forming unit; MPN = Most-probable-number; MFHPB = Microbial Analysis of Food Health Protection Branch; MFLB = Microbiological Food Laboratory Procedure.

[1] Based upon dried solids.

[2] AOAC. 2000. Chapter 44. Sugars and Sugar Products. 44.1.03. AOAC Official method 925.45. Moisture in Sugar. A. Vacuum Drying. Official Methods of Analysis of the Association of Official Analytical Chemists (17th Ed.). Association of Official Analytical Chemists (AOAC); Arlington, Virginia. Vols. 1&2. (2002, Revision 1). pp.1-2.

[3] USP. 2005. Test Methods <211> Arsenic, <241> Lead, <281> Residue on Ignition. United States Pharmacopeia (28th Ed.) & National Formulary (23rd Ed.). U.S. Pharmacopeia (USP) Convention Inc.; Rockville, Maryland. pp. 2297-2298, 2300-2301, and 2303.

III. Self-Limiting Levels of Use

The use of Vitasugar™ in food is largely limited by the desired sweetness intended for a particular food or beverage product. Thus, the use of Vitasugar™ in foods at upper use-levels is largely self-limiting based on its organoleptic properties.

IV. Basis for GRAS Determination

Pursuant to 21 CFR §170.35, Vitasugar™ (syrup and powder), under the intended conditions of use specified herein and defined in Appendix I **[EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF VITASUGAR™, AN ISOMALTO-OLIGOSACCHARIDE (IMO) MIXTURE, FOR USE IN FOODS]** has been determined by BioNeutra to be GRAS on the basis of scientific procedures (U.S. FDA, 2007b). This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of Vitasugar™ as a component of food.

Isomalto-oligosaccharides occur naturally in the diet as constituents of fermented foods (*e.g.*, rice miso, soy sauce, and sake) (Hondo and Mochizuki, 1979; Nishino *et al.*, 1981; Nunokawa, 1981; Tungland and Meyer, 2002). The disaccharide, isomaltose, is a normal constituent of honey (White and Hoban, 1959).

The evaluation of the safety of BioNeutra's IMO products is primarily based on well-established metabolic profiles for the simple saccharide components of the mixture (*e.g.*, maltose,

isomaltose), as well as animal and human studies assessing the digestion and elimination of the larger oligomers. Malto-oligomers (1→4), as well as some of the smaller isomalto-oligomers (1→6) such as isomaltose are digested by intestinal enzymes to glucose, which is taken up systemically and utilized in normal physiological pathways. Accordingly, consumption of malto-oligosaccharides and smaller digestible isomalto-oligosaccharides is not expected to be associated with any adverse effects. Conversely, the larger isomalto-oligosaccharides will pass essentially undigested through the gastrointestinal tract and are subjected to bacterial fermentation in the colon. The lack of absorption of the larger isomalto-oligosaccharides largely limits the potential for the occurrence of any systemic toxicity.

While toxicity is not expected by virtue of the disposition of the oligosaccharides (breakdown to glucose or fermentation in the colon), in assessing the safety of BioNeutra's IMO products, results of several published and unpublished short- and long-term animal toxicity studies conducted with similar IMO mixtures were reviewed. Pre-clinical data included a long-term oral toxicity study in which no adverse effects were observed in rats following administration of an isomalto-oligoasccharide product for a period of 1 year (Kaneko *et al.*, 1990). Consumption of non-digestible materials that are subjected to bacterial fermentation in the lower colon may lead to gastrointestinal discomforts (*e.g.*, increased flatulence and bloating). As such, a series of published human studies was identified which demonstrated that isomalto-oligosaccharides are well-tolerated at levels reflective of the intended conditions of use (Kohmoto *et al.*, 1988; Kaneko *et al.*, 1993; Chen *et al.*, 2001; Wang *et al.*, 2001; Oku and Nakamura, 2003; Bouhnik *et al.*, 2004). A number of the human studies also included clinical chemistry parameters that provided further support for safety of the ingredient.

Compositional comparison of the test materials used in the animal and human studies and Vitasugar™ revealed a wide distribution in the saccharide profiles among the individual IMO products. The variations in the composition among various products consisted primarily of differences in the percent distribution of specific oligomers [*i.e.*, proportion of smaller (mono- and di-saccharides) *vs.* larger oligosaccharides (tri-, tetra-, penta-oligosaccharides *etc.*) and proportion of malto- (1→4) *vs.* isomalto- (1→6) oligosaccharides]. Such variations in the saccharide profile of the IMO products will primarily affect what fraction of the test material is digested to glucose, *versus* the amount that will be available for bacterial fermentation. Results of studies performed with IMO products with an oligomer profile dominated by larger isomalto-oligosaccharides are appropriate for the evaluation of potential gastrointestinal disturbances that could result from the consumption and breakdown of the larger isomalto-oligosaccharides in the colon. As such, studies performed with products of slightly differing saccharide composition than that of Vitasugar™ were considered to be relevant to the overall assessment of its safety.

Since non-digestible oligomers may affect the absorption of nutrients (*i.e.*, minerals), the composition of the microflora, with secondary effects on colonic short-chain fatty acid production, and enhance bile acid excretion, a number of studies preformed to assess specifically the

nutritional implications of consuming isomalto-oligosaccharides also were considered in the evaluation of the safety of Vitasugar™.

Using these data to support the safety of the ingredient, Vitasugar™ is GRAS based on scientific procedures. A summary of this information is provided in Appendix I **[EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF VITASUGAR™, AN ISOMALTO-OLIGOSACCHARIDE (IMO) MIXTURE, FOR USE IN FOODS]**.

V. References

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APPENDIX I

EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF VITASUGAR™, AN ISOMALTO-OLIGOSACCHARIDE (IMO) MIXTURE, FOR USE IN FOODS.

EXPERT PANEL REPORT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF VITASUGAR™, AN ISOMALTO-OLIGOSACCHARIDE (IMO) MIXTURE, FOR USE IN FOODS

March 12, 2007

Introduction

At the request of BioNeutra Inc. (hereafter BioNeutra) an Expert Panel (the "Panel") of independent scientists, qualified by their relevant national and international experience and scientific training to evaluate the safety of food ingredients, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and determine whether, under the conditions of intended use in food as an alternative sweetener, Vitasugar™ (syrup or powder), an isomalto-oligosaccharide (IMO) product, would be Generally Recognized as Safe (GRAS), based on scientific procedures. The Panel consisted of Professors Joseph F. Borzelleca, Ph.D. (Medical College of Virginia), John Doull, M.D., Ph.D. (University of Kansas Medical Center), and Robert Nicolosi, Ph.D. (University of Massachusetts, Lowell). *Curricula vitae* evidencing the Panel members' qualifications for evaluating the safety of food ingredients are provided in Attachment 1.

The Panel, independently and collectively, critically examined a comprehensive package of publicly available scientific information and data compiled by Cantox Health Sciences International from the literature and other published sources through December 2006. In addition, the Panel evaluated other information deemed appropriate or necessary, including data and information provided by BioNeutra. The data evaluated by the Panel included information pertaining to the method of manufacture and product specifications, analytical data, intended use-levels in specified food products, and consumption estimates for Vitasugar™, as well as comprehensive literature on the safety of isomalto-oligosaccharides.

Following independent and collective critical evaluation of such data and information, the Panel unanimously concluded that under the conditions of intended use in traditional foods described herein, meeting appropriate food-grade specifications, and manufactured and used in accordance with current good manufacturing practice (cGMP), Vitasugar™, a product consisting of a mixture of isomalto-oligosaccharides, is GRAS based on scientific procedures. A summary of the basis for the Panel's conclusion is provided below.

Composition, Manufacturing, and Specifications

The term "oligosaccharide" encompasses carbohydrates that are larger than simple di- or tri-saccharides, but smaller than polysaccharides (greater than 6 units). Isomalto-oligosaccharides, specifically, are glucose oligomers with α-D-(1,6)-linkages, including among others isomaltose, panose, isomaltotetraose, isomaltopentaose, nigerose, kojibiose, and higher branched oligosaccharides (PDRNS, 2001). While human intestinal enzymes readily digest α-(1,4)-glycosidic bonds, α-(1,6)-linkages, particularly those linking longer polymers, are not easily hydrolyzed as they pass through the human gastrointestinal tract. The majority of oligosaccharides found in Vitasugar™ consist of 3 to 6 monosaccharide units linked together; however, disaccharides, as well as longer polysaccharides (up to 9 units) also are present. The disaccharide fraction of Vitasugar™ consists of the α-1→4 linked maltose and the α-1→6 linked isomaltose, while maltotriose, panose, and isomaltotriose make up the trisaccharide fraction. Isomaltotetraose, isomaltopentaose, isomaltohexaose, isomaltoheptaose, and small amounts of oligomers with 8 or more degrees of polymerization comprise the remaining oligomers in Vitasugar™. Based on the composition of sample lots, Vitasugar™ (syrup or powder) contains between 15 and 20% of smaller saccharides with fewer than 3 glucose units. Oligosaccharides with 3 to 6 degrees of polymerization comprise approximately 70 to 80% of the product's composition. Larger oligomers of 7 or more glucose units, account for not more than 10% the saccharide composition.

Vitasugar™ is produced in accordance with cGMP *via* enzyme-catalyzed hydrolysis of corn, wheat, rice, cassava, barley, oats, potato, pulses (*e.g.*, peas, beans, lentils, *etc.*), and other starch material sources. Specifically, an α-glucosidase from *Aspergillus niger* (transglucosidase L "Amano"), α-amylases of fungal and bacterial origin (*Aspergillus oryzae* and *Bacillus licheniformis*, respectively), and a pullulanase from *Bacillus acidopullulyticus* are added to the starting starch slurry (starch and water) to progressively hydrolyze the amylose and amylopectin polysaccharides that make up the starch to produce mono-, di-, tri-, and other smaller oligosaccharides with α-(1,4)- and α-(1,6)-glycosidic linkages. Monosaccharides (glucose) that have formed during the process are removed by the addition of dried yeast (*Saccharomyces cerevisiae*). The alcohol (ethanol) that forms as a by-product of the fermentation reaction evaporates as the temperature is increased to at least 90°C to terminate the reaction. Several down-stream purification steps are employed in the manufacturing of Vitasugar™ to minimize the potential for the occurrence of any residues of the biocatalysts or other processing aids used during the production process in the final products. The final product is available in both syrup and powder form. The syrup and powder Vitasugar™ products display a light-sweet taste. While the syrup is a pale yellow or colorless transparent liquid of a sticky consistency, the powder appears white in color.

All starting materials (*e.g.*, wheat, barley, oat, and potato starch) and processing chemicals are appropriate for use in food and meet the specifications of the Food Chemicals Codex, 5th Edition (FCC, 2003). The specifications for the different enzyme and yeast preparations used during the production of Vitasugar™ are consistent with those of the Joint FAO/WHO Committee on Food Additives (JECFA, 1991) and/or FCC (2003). Transglucosidase L "Amano", which is obtained from *A. niger* and catalyzes the conversion of the α-(1,4)-glycosidic bonds into α-(1,6)-glycosidic bonds to form 1,6-linked oligosaccharides, has been previously determined to be GRAS based on scientific procedures for use in the production of branched oligosaccharides at levels of up to 0.14% (v/w) (Matsuura *et al.*, 1998). The U.S. Food and Drug Administration (FDA) expressed no objections in response to notifications regarding the GRAS status of fungal α-amylase from *A. oryzae* and pullulanse from *B. acidopullulyticus* (U.S. FDA, 2002). Bacterial α-amylase (from *B. licheniformis*) and dried yeast cells (from *S. cerevisiae*) are approved for use in food in the U.S. (U.S. FDA, 2007a,b).

The physical and chemical specifications for Vitasugar™, syrup and powder, are presented in Table 1-A; the microbiological specifications appear in Table 1-B. Analysis of representative lots demonstrated compliance with final product physical, chemical, and microbiological specifications.

Although the ethanol that may have formed during the manufacturing process will evaporate as the temperature of the reaction mixture is increased to terminate enzymatic activity, several lots of the final product were analyzed for residual ethanol content. No detectable levels of ethanol (limits of quantification – 5 ppm) were identified in any of the sampled lots.

Stability

Study results have demonstrated that Vitasugar™ remains stable following storage for up to 14 weeks at pH 2 (room temperature). Vitasugar™ (powder or syrup) is expected to be as stable as other similar already marketed commercial monosaccharide/oligosaccharide sweetener products. Microbial growth is largely prevented as a result of the low moisture content of the product. In case that the product was to undergo degradation, progressively smaller saccharides and glucose units would be expected to form.

Intended Uses

Isomalto-oligosaccharides are normal components of the human diet that occur naturally in a number of fermented foods, including rice miso, soy sauce, and sake (Hondo and Mochizuki, 1979; Nishino *et al.*, 1981; Nunokawa, 1981; Tungland and Meyer, 2002). Isomaltose, one of the 1→6 linked disaccharide components of Vitasugar™, has been identified as a natural constituent of honey (White and Hoban, 1959; White *et al.*, 1961).

Vitasugar™ is characterized by a sweetness 40 to 60% relative to that of sucrose. BioNeutra proposes to market Vitasugar™ (syrup and powder), as an alternative sweetener for partial replacement of other currently available sweeteners at levels providing up to 15 g per serving [Reference Amounts Customarily Consumed Per Eating Occasion (RACC) (U.S. FDA, 2007c)] in several conventional foods. The individual proposed food-uses and use-levels for Vitasugar™ are summarized in Table 2. Serving sizes were assigned according to Title 21, Section §101.12, RACC (U.S. FDA, 2007c).

Exposure Estimates

Two different approaches were used to calculate consumption estimates for Vitasugar™. In the first case, consumption of Vitasugar™ was based on production volume estimates. Production volume of an ingredient and the disappearance of the produced amount into the food supply of a defined population size (*e.g.*, U.S. population) over a specified period of time (*e.g.*, annually) can be used as an indicator of the consumption of the food ingredient by consumers (*i.e.*, *per capita* intake). Based on actual projected production of Vitasugar™ of 16,000 tons by 2010, the *per capita* intake was estimated to be approximately 0.2 g/person/day.

Alternatively, in the second scenario, intake estimates were determined based on the replacement of 2 servings per day of sucrose containing foods with Vitasugar™. Assuming daily consumption of 2 servings of food with added Vitasugar™ at the proposed use-levels as indicated in Table 2, an intake estimate of not more than 30 g/person/day was calculated.

The use of Vitasugar™ in food is largely limited by the desired sweetness intended for a particular product. Thus, the use of Vitasugar™ in foods at upper use-levels is largely self-limiting based on its organoleptic properties.

Safety Assessment

Overview

The evaluation of the safety of Vitasugar™ was primarily based on well-established metabolic profiles for the simple saccharide components of the mixture (*e.g.*, maltose, isomaltose), as well as animal and human studies assessing the digestion and elimination of the larger oligomers present in the IMO products. Additionally, in assessing the safety of Vitasugar™, results of several short- and long-term animal toxicity studies conducted with similar IMO mixtures also were reviewed. Although the exact composition of the IMO preparations evaluated in the studies that were reviewed by the Panel in support of the safety of Vitasugar™ differed somewhat from the oligomer profiles of the Vitasugar™ products, these studies are considered to be nonetheless relevant to the overall assessment of the safety of Vitasugar™. Firstly, since the production of IMO mixtures occurs *via* natural enzymatic processes, some compositional variability between different products is expected. Furthermore, variations in the composition among various products consisted primarily of differences in the percent distribution of specific oligomers. For example, some IMO products were characterized by a larger disaccharide fraction than the level of disaccharides found in Vitasugar™. Wherever provided, the composition reported for a particular test material used in a study that was reviewed as part of this evaluation of IMO safety, was compiled separately in Table 3.

Given the sequential hydrolysis of the malto-oligomers (1→4) and some of the smaller isomalto-oligomers (1→6) such as isomaltose to glucose, a basic intermediate of carbohydrate metabolism, consumption of malto-oligosaccharides and smaller digestible isomalto-oligosaccharides is not expected to be associated with any adverse effects. Since the larger isomalto-oligosaccharides will pass essentially undigested through the gastrointestinal tract, lack of absorption largely limits the potential for systemic toxicity; however, microbial fermentation of the "isomalto" constituents in the colon will be accompanied by production of short-chain fatty acids and various gaseous by-products, possibly leading to gastrointestinal discomforts (*e.g.*, increased flatulence and bloating). As such, a number of human tolerance studies also were evaluated. Non-digestible oligomers may affect the absorption of nutrients (*i.e.*, minerals), the microflora with secondary effects on colonic short-chain fatty acid production, and enhance bile acid excretion. Accordingly, a number of studies performed to assess specifically the nutritional implications of consuming isomalto-oligosaccharides were reviewed by the Panel.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Isomalto-oligosaccharide preparations such as Vitasugar™ consist of a mixture of malto- and isomalto-oligosaccharides, as well as smaller saccharides including maltose, isomaltose, and panose. The smaller isomalto-saccharides, such as isomaltose, as well as the malto-

oligosaccharides are subject to enzymatic hydrolysis. Although 1→6 linked oligomers escape digestion in the mouth *via* salivary α-amylase, a number of enzymes have been identified in the epithelial cells of the brush border of the intestinal mucosa, which are capable of hydrolyzing di- and larger oligosaccharides, including smaller saccharides with (1,6)-bonds (Würsch, 1991). These enzymes include the sucrase-isomaltase complex, glycoamylase, and lactase. Sucrase-isomaltase is an intestinal enzyme that consists of 2 subunits with one cleaving α-(1,4)-glycosidic linkages and the other the α-(1,6)-linkages to release individual glucose molecules (Dahlqvist *et al.*, 1963; Würsch, 1991; Heymann *et al.*, 1995; Oku and Nakamura, 2003). Glucose, produced as a result of the hydrolysis of the digestible saccharides, is absorbed and used by the body as a source of energy.

While no hydrolysis occurred in an *in vitro* model system containing artificial gastric juice or α-amylase (human salivary or hog pancreatic), hydrolysis of a mixture of isomalto-oligosaccharides was observed in the presence of rat intestinal mucosa enzymes, albeit at a markedly lower rate than with maltose or isomaltose alone (Kaneko *et al.*, 1992). In an *in situ* investigation, the rat jejunum loop method was used to compare the digestibility of an IMO mixture to several other oligosaccharides, including a mixture consisting predominantly of digestible saccharides (IMO-2), another mixture enriched in highly polymerized isomalto-oligosaccharides (IMO-3), hydrogenated IMO (H-IMO), and other non-digestible saccharides such as fructo-oligosaccharides (FOS) (Kaneko *et al.*, 1995). The rate of luminal clearance, from fastest to slowest, was determined to be as follows: maltose > IMO-2, sucrose, maltotriose > IMO mixture> IMO-3 > H-IMO, maltitol, FOS, raffinose.

In 6 healthy male subjects, approximately 30 and 60% of administered radioactivity was recovered in expired CO_2 over 8 to 12 hours following oral ingestion of 50 mg of a radiolabeled IMO preparation and 25 g of an unlabelled IMO mixture at rest and before intermittent exercise, respectively (Kohmoto *et al.*, 1992). Given the appearance of peak levels of radioactive CO_2 in the breath samples at 2 to 3 hours following consumption, it is expected that the expired $^{13}CO_2$ levels resulted from the metabolism of absorbed glucose, rather than from colonic fermentation. Since microbial fermentation in the lower gastrointestinal tract is the only source of hydrogen gas (H_2) production in humans (Calloway *et al.*, 1966; Levitt, 1969; Muir *et al.*, 1995), excretion of breath hydrogen following consumption of IMO mixtures also can be used to assess the fermentability of the oligosaccharides (Calloway, 1966). In total, 13.0±0.8 and 15.2±1.0 mL of breath hydrogen (H_2) was evolved during the sedentary state and exercise trial, respectively, with H_2 expiration increasing over the course of the exercise period, but remaining constant for the duration of the sedentary trial. In comparison, ingestion of an unspecified, but presumably comparable amount of the sugar alcohol, maltitol (4-O-α-glucopyranosyl-D-sorbitol), resulted in the expiration of 52.9±6.5 mL of hydrogen (Tsuji *et al.*, 1992 as cited in Kohmoto *et al.*, 1992), suggesting that only about 25% of the ingested IMO mixture was fermentable compared to maltitol. Furthermore, significantly increased serum glucose and insulin levels were observed at

30 minutes following consumption of the IMO mixture in sedentary subjects, as well as during exercise. Significant reductions in levels of nonesterified fatty acids (NEFA) were noted for the first 60 to 90 minutes (30 minutes in the sedentary test) after IMO ingestion at rest and before exercise. No isomalto-oligosaccharides were recovered in stool samples collected from 3 subjects for 3 days after dosing.

Breath hydrogen expiration also was used to compare the fermentability of a mixture of isomalto-oligosaccharides to other oligosaccharides (*i.e.*, FOS and galactosyl-sucrose) in another human trial (9 males and 29 females) (Oku and Nakamura, 2003). The area under the curve (AUC) (420 minutes *vs.* hydrogen excretion, in ppm) obtained following consumption of an oral 10 g dose of an IMO product dissolved in water (AUC: approximately 830 ppm), was significantly lower in comparison to AUCs obtained following ingestion of equal doses (10 g) of the other oligosaccharides, FOS and galactosyl-sucrose (AUCs: approximately 9,800 and 3,700 ppm, respectively). Furthermore, ingestion of 20 g of the IMO mix produced only a marginal increase in hydrogen excretion (1.4-fold) in comparison to the 10 g dose, whereas doubling of the FOS or galactosyl-sucrose doses increased breath hydrogen excretion 1.7 to 2.7 times. The AUC obtained when 40 g of the IMO mixture was ingested (AUC: 2,440 ppm) was still lower than the AUC values obtained with only 10 g of either FOS or galactosyl-sucrose.

Toxicological Studies

Acute Studies

In male Wistar rats, an IMO mixture consisting of di-, tri, and larger oligosaccharides (*i.e.*, 52.5, 25.4, and 15.2%, respectively) exhibited a very low order of acute oral toxicity with LD_{50} values estimated to be greater than 44 g/kg body weight (Kaneko *et al.*, 1990). Two (2) of the 6 treated rats died at the 44 g/kg body weight dose level.

Subchronic Studies

Results of short- and long-term toxicity studies in which rats were administered IMO products in the diet or in the drinking water are summarized in Table 4 and are described briefly below.

In a short-term animal study in which several different digestible and non-digestible sugars were compared, a group of 8 male Sprague-Dawley rats was administered 20% of an IMO mixture in the diet (approximately 20 g/kg body weight/day) for a period of 35 days (Kaneko *et al.*, 1992). In comparison to the basal diet (corn starch) control group, final body weights, body weight gain, and food intake of IMO-treated rats were slightly reduced, but not at levels of statistical significance. A statistically significant decrease was, however, observed in the food utilization efficiency of IMO-treated rats. Relative weights of a series of major organs including the liver in rats treated with the IMO mixture were comparable to those reported in the basal diet controls.

In a 6-week study groups of 5 to 6, 2-month-old male Sprague-Dawley rats were administered a mixture of isomalto-oligosaccharides in the diet at concentrations of 0, 5, 10, or 20% (approximately 0, 5, 10, and 20 g/kg body weight/day, respectively) (Day and Chung, 2004). No significant variations were observed in the weight gain and food intake of IMO-treated rats compared to the untreated basal diet controls; however, administration of the mixture of dietary isomalto-oligosaccharides was associated with a positive trend for increased food consumption. With the exception of increased cecal weights in mid- and high-dose animals, weights of a series of other major organs (heart, spleen, kidneys, lungs, and brown and white adipose tissue) were comparable to controls. The authors considered the increases in cecal weights as likely related to an increase in the colonic bacterial population. Additionally, a dose-dependent reduction (statistical significance not specified) in abdominal fat (gram abdominal fat/gram food intake) was reported in rats fed the IMO mix in the diet.

In a single-dose study, a group of 8 male Wistar rats received 3% of an IMO product in drinking water providing daily dose levels in the range of approximately 3 to 5 g/kg body weight for a period of 12 months (Kaneko *et al.*, 1990). At study completion, blood samples were obtained for standard clinical chemistry testing and animals were killed for histopathological examination. Additionally, interim clinical evaluations also were conducted at months 1, 3, and 6. Body weights of IMO-treated males remained comparable to those of control animals during the treatment period. At study completion, significant variations in hematology and clinical chemistry parameters were limited to decreases in levels of hemoglobin, hematocrit, and alanine aminotransferase (ALT) in test animals compared to controls; however, neither the gross necropsy nor the histopathological examination revealed any abnormalities related to the administration of the IMO preparation. In additional detailed analysis of white blood cell levels conducted to determine any potential immune stimulatory effects, no changes were observed in the absolute number of white blood cells of test rats relative to levels reported in the control group, whereas significant variations in total and individual subgroups of lymphocytes (*i.e.*, elevated levels of total lymphocytes, total T cells, B cells, and helper and suppressor T cells) were limited to the first treatment month.

A few other short-term studies up to 35 days in duration were conducted with physiologically normal, as well as diabetic male Sprague-Dawley rats, which were designed primarily to assesses the potential effects of IMO preparations on metabolic end-points and intestinal physiology, but which also included determinations of body weights and body weight gain, food intake, and liver and/or kidney weights (Ly *et al.*, 1999; Chai and Rhee, 2001; Sung *et al.*, 2004). Differences observed between the rats receiving IMO mixtures in the diet at concentrations in the range of 6 to 12% (approximately 3 to 10 g/kg body weight/day, respectively) and controls were largely limited to increased weights of the cecum or cecal contents (Ly *et al.*, 1999; Chai and Rhee, 2001; Sung *et al.*, 2004). Although in comparison to a control group, the increase in relative cecal content weight in rats administered the IMO

preparation at 12% in the diet (sponge cakes with 40% of the sucrose content replaced by IMO mix and added to diet at 30%) for a period of 25 days was not statistically significant, significant variations were observed in the cecal content pH (decreased), dry fecal weight (increased), and fecal water content (increased) (Ly *et al.*, 1999).

Genotoxicity Studies

Evaluated *in vitro* in a standard battery of *Salmonella typhimurium* (*i.e.*, TA98, TA100, TA1535, and TA1537) and in *Escherichia coli* WP2*uvr*A with and without metabolic activation, the IMO product did not induce significant increases in the number of revertant colonies at concentration of up to 10% per plate (Kaneko *et al.*, 1990). Likewise, the IMO mixture failed to significantly increase the number of chromosome aberrations in Chinese hamster lung (CHL) cells at concentrations of up to 3% in either the absence or presence of a bioactivation system following a 24- or 48-hour incubation period (Kaneko *et al.*, 1990).

Human Tolerance Studies

Several human studies ranging from 7 to 35 days in duration that were primarily designed to assess various indices related to the putative prebiotic properties of IMO preparations, also evaluated their tolerability. Results of these studies are presented in detail in Table 5. Additionally, several authors have reported a threshold value of 1.5 g/kg body weight or greater (approximately 90 g in the case of a 60 kg individual) for the induction of transient diarrhea resulting from the consumption of single bolus doses of isomalto-oligosaccharides (Oku and Okazaki, 1999; Oku and Nakamura, 2002).

While ingestion of single 20 g doses of FOS or galactosyl-sucrose induced various abdominal discomforts (*e.g.*, distention, borborygmus, flatus), no gastrointestinal disturbances were observed following consumption of up to 40 g of an IMO product (Oku and Nakamura, 2003). Similarly, no gastrointestinal symptoms were reported by study participants following repeat ingestion of an IMO mixture at dose levels of 10 to 15 g for a period of 3 weeks, with a 1-week IMO-free interval between 2 consecutive weeks of treatment followed by another 7 days of IMO-ingestion (Kaneko *et al.*, 1993).

Conversely, in 2 other studies, increases were reported in the severity or incidence of various gastrointestinal symptoms (*e.g.*, flatulence, abdominal pain and distension, bargorygmi) following consumption of 20 or 30 g of IMO preparations for 10 or 28 days in comparison to baseline levels; however, in none of these studies did the study subjects experience increased incidences or severity of diarrhea (Kohmoto *et al.*, 1988; Wang *et al.*, 2001). Moreover, increased flatulence reported by individuals in the study conducted by Kohmoto *et al.* (1988) was only temporary and subsided with treatment, suggesting that the microfloral population adapted to changes in the amount of undigested material passing into the colon. In a study

conducted with a group of elderly men with a history of chronic constipation, a 3-fold increase in defecation frequency and significantly greater wet and dry fecal weight per day and per stool sample were reported following consumption of an IMO preparation for a period of 30 days at dose levels of up to 24 g in comparison to a 30-day control period; however, changes in bowel movements and stool characteristics were not accompanied by any reports of gastrointestinal discomforts (Chen *et al.*, 2001). Moreover, in a placebo-controlled, double-blind study, gastrointestinal disturbances in subjects consuming daily 10 g of an IMO preparation for a period of 7 days increased only in comparison to a 7-day run-in period, but not in comparison to the placebo (Bouhnik *et al.*, 2004). None of the subjects experienced diarrhea.

In 2 studies which also included evaluations of clinical biochemistry, no significant variations were observed in several clinical chemistry parameters (*e.g.*, total protein, albumin, blood urea nitrogen, creatinine) when elderly subjects or hemodialysis patients were provided daily 24 or 30 g of an IMO preparation for 30 and 28 days, respectively (Chen *et al.*, 2001; Wang *et al.*, 2001). In comparison to pre-treatment values, the hemodialysis patients did, however, exhibited elevated hemoglobin and hematocrit values following ingestion of the IMO mixture, which as suggested by the authors may have been at least in part due to enhanced iron absorption (Wang *et al.*, 2001).

Nutritional Safety Issues

Consumption of non-digestible carbohydrates has been related to several nutritional effects, including changes in the microflora, increases in short-chain fatty acid production, enhanced bile acid excretion, and changes in mineral bioavailability. Accordingly, these were addressed individually in relation to the ingestion of isomalto-oligosaccharides.

Changes in Colon Microflora

Unlike probiotics which are broadly defined as living microorganisms that may beneficially affect the host upon ingestion by improving the balance of the intestinal microflora, prebiotics are non-digestible food ingredients that may have positive effects on the host by selectively stimulating the growth and/or activity of certain bacteria in the colon (PDRNS, 2001). Studies conducted to assess the digestibility of IMO mixtures indicate that the oligosaccharides are at least partially fermented by bacteria in the colon. Consequently, the unhydrolyzed and, therefore, unabsorbed portion of an IMO mixture reaching the colon may stimulate the growth of bacterial subpopulations. Generally, however, this is regarded as a beneficial, rather than an adverse effect.

Examined *in vitro*, mixtures of isomalto-oligosaccharides were shown to increase levels of bifidobacteria (Kohmoto *et al.*, 1988; Rycroft *et al.*, 2001), but only few other human bacterial species (Kohmoto *et al.*, 1988). In rats and mice, repeat administration of IMO mixtures in the

diet was associated with increases in *Bifidobacterium* and *Lactobacillus* levels, paralleled by reductions in the growth of *Clostridium* species (Kaneko *et al.*, 1990; Qing *et al.*, 2003).

Results of human linear studies (*i.e.*, comparison of pre- and post-treatment levels of colonic bacteria) provide evidence to suggest that consumption of IMO mixtures at dose levels of 10 to 24 g over periods of several days (*i.e.*, 10 to 30 days) increased levels of bifidobacteria in the colon (Kohmoto *et al.*, 1988; Kaneko *et al.*, 1993; Chen *et al.*, 2001). Based on significant increases observed in the levels of fecal bifidobacteria following ingestion of 13 or 15 g of an IMO product, but not at lower doses of 7 or 10 g for periods of 10 days, Kohmoto *et al.* (1991) determined 8 to 10 g of isomalto-oligosaccharides (*i.e.*, the IMO content in 13 and 15 g of the IMO test product, respectively) to be the minimum effective dose for the improvement of intestinal microflora.

However, a placebo-controlled study with human subjects did not confirm these results (Bouhnik *et al.*, 2004). Specifically, following a 7-day treatment period, no statistically significant differences were observed in the fecal levels of bifidobacteria between subjects ingesting daily a total of 10 g of an IMO mixture and the placebo group. Results of the study conducted by Bouhnik *et al.* (2004) suggest that the majority of the IMO mixture is efficiently hydrolyzed to glucose upon consumption. It should be noted, however, that the composition of the IMO product used in this study was not identified and, thus, the possibility that the mixture used in the placebo-controlled study differed from the IMO products used in the linear studies (*e.g.*, was characterized by a larger content of digestible material) cannot be excluded.

Short-Chain Fatty Acid (SCFA) Production

Non-digestible oligosaccharide, escaping hydrolysis and absorption in the small intestine, are fermented in the colon by intestinal bacteria. In addition to hydrogen, other products of bacterial fermentation include carbon dioxide (CO_2), methane (CH_4), water, lactic acid, and short-chain fatty acids such as acetate, propionate, and butyrate. Presently there is conflicting evidence regarding the effects of increased levels of butyrate production in the lower segments of the gastrointestinal tract. While a number of *in vitro* and *in vivo* studies have suggested that production of butyrate stimulates cell growth (Sakata, 1987; Gibson *et al.*, 1992), which may be pro-carcinogenic due to the increased probability of errors (mutations) occurring in the newly replicated DNA of colonocytes, human studies suggest that butyrate is protective and that it reduces the risk of colon cancer (Burn *et al.*, 1995; Cummings, 1995; Mathers, 1998; Topping and Clifton, 2001).

Levels of fecal short-chain fatty acid levels were measured in a few of the animal and human studies to determine whether ingestion of IMO products resulted in changes in short-chain fatty acid production. While an increase was observed in lactate and acetate levels in an *in vitro* study in which fecal bacteria were incubated with isomalto-oligosaccharides, no variations were

observed in propionate and butyrate levels (Rycroft *et al.*, 2001). Conversely, in a pre-clinical rat study, no changes were observed in levels of individual short-chain fatty acids or in the pH level of the cecum following administration of 5% of an IMO mixture in the diet (approximately 2.5 g/kg body weight; unspecified period of time) in comparison to a control group (Ohta *et al.*, 1993). Meanwhile, in rats provided FOS in the diet at 5%, significant reductions were observed in cecal pH and acetate and propionate levels, accompanied by increased levels of D- and L-lactate and butyrate (IMO group only) relative to the control and IMO-treated groups.

In human studies, results were generally more comparable to those observed in the *in vitro* assays, with increases noted in total short-chain fatty acid levels, but not in butyrate following daily ingestion of 10 to 24 g of IMO-containing mixtures for a period of 21 to 30 days in comparison to pre-treatment values (Kaneko *et al.*, 1993; Chen *et al.*, 2001). In the trial conducted by Chen *et al.* (2001), increases also were observed in individual short-chain fatty acids (*i.e.*, acetate and propionate).

Since increases in the presence of short-chain fatty acids, resulting from the degradation of non-digestible carbohydrates in the large intestine are expected to be associated with lower pH levels in the colon (Walker *et al.*, 1979), the absence of any significant changes in the acidity of the colonic content in most linear studies, as well as in the placebo-controlled study in which IMO products were provided to study participants at dose levels of 7 to 24 g for up to 30 days (Kohmoto *et al.*, 1991; Chen *et al.*, 2001; Bouhnik *et al.*, 2004), suggests that the IMO products mediate little if any changes in short-chain fatty acid production. The study in which 15 g of an IMO product (10 g isomalto-oligosaccharides) was ingested by study subjects for a period of 14 days provides the only exception (Kohmoto *et al.*, 1991). Specifically, in comparison to the pre-treatment values (pH 7.3), the pH was reduced significantly to 6.6 at the end of the 14-day trial.

Increased Bile Acid Secretion

Presence of increased amounts of undigested material in the colon has been also related to greater bile acid excretion in the stool; however, in a single rat study in which fecal bile acid excretion was measured in Sprague-Dawley rats provided an IMO mix in the diet at a concentration of 6% (3 g/kg body weight/day) for a period of 5 weeks, only a slight (less than 10%) and not statistically significant increase was observed in total bile acid excretion (Sung *et al.*, 2004). Likewise, daily fecal excretion of individual neutral steroids (*i.e.*, cholesterol, coprostanol, and coprostanone) of IMO-treated rats was comparable to controls. In rat studies in which plasma cholesterol levels were assessed as an indirect measure of changes in bile acid secretion, no changes were observed between rats administered IMO mixtures in the diet for a period of up to 12 months at dose levels in the range of 5 to 20 g/kg body weight/day and controls (Kaneko *et al.*, 1990, 1992; Ly *et al.*, 1999; Chai and Rhee, 2001). In contrast, in humans, significant reductions were observed in serum triglyceride and total cholesterol levels, in association with increased high-density lipoprotein (HDL)-cholesterol levels following daily

consumption of 30 g of an IMO mixture for a period of 28 days compared to pre-treatment values in one trial (Wang *et al.*, 2001), but remained comparable to baseline levels in another 30-day study following consumption of 24 g of an IMO product (Chen *et al.*, 2001).

Mineral Binding

It has been reported that consumption of various dietary fibers may reduce mineral bioavailability, by binding the minerals and forming insoluble complexes, thereby resulting in decreased mineral absorption and increased fecal mineral excretion (Pilch, 1987). Alterations in the colonic environment (*e.g.*, decreases in pH levels) as a result of increased bacterial fermentation of non-digestible carbohydrates and secondary changes in short-chain fatty acid levels have been implicated in ensuing changes in mineral absorption. In the only study in which absorption of several minerals (*i.e.*, calcium, magnesium, and phosphorus) was assessed in rats provided diets supplemented with 5% of an IMO mixture (unspecified period of time), mineral absorption of IMO-treated rats did not differ from controls (Ohta *et al.*, 1993). Enhanced iron absorption as a result of ingestion of an IMO product was suggested as a possible reason for the increases observed in hemoglobin and hematocrit values in hemodialysis patients (Wang *et al.*, 2001).

Summary

Vitasugar™ consists of a mixture of isomalto-oligosaccharides and is proposed for use as an alternative sweetener as a partial replacement for currently available sweeteners in a variety of food products including baked goods and baking mixes, beverages and beverage bases, breakfast cereals, condiments and relishes, dairy product analogs, mayonnaise and mayonnaise-type dressings, salad dressings, frozen dairy deserts and mixes, gelatins, puddings, and fillings, gravies and sauces, hard and soft candies, jams and jellies, milk and milk products, meat and nut products, processed fruits and vegetables and fruit and vegetable juices, snack foods, sugar substitutes, sweet sauces, toppings, and syrups, and meal replacement bars and mixes. Based on the body weight-to-food intake ratio of rats treated with a mixture of isomalto-oligosaccharides for a period of 35 days and expiration of CO_2 by sedentary and active human subjects following consumption of an IMO preparation, the nutritive value of IMO preparations was estimated to be approximately 2.7 to 3.3 kcal/g or 70 to 80% relative to that of maltose (Kaneko *et al.*, 1992; Kohmoto *et al.*, 1992). Vitasugar™ is proposed for use at use-levels of up to 15 g/serving. Based on 1996 production volume estimates of all sweeteners and assuming 5% replacement of all sweeteners with Vitasugar™, the *per capita* intake was estimated to be 7 g Vitasugar™/person/day; however, based on the anticipated production volume of Vitasugar™ by 2010, the *per capita* intake is estimated to be only 150 mg Vitasugar™/person/ day. Alternatively, assuming that a person will consume 2 servings of food per day to which Vitasugar™ has been added at levels of up to 15 g/serving, a daily intake level of not more than 30 g Vitasugar™/person is estimated.

Vitasugar™ is produced *via* the enzymatic degradation of corn, wheat, rice, cassava, barley, oats, potato, pulses (*e.g.*, peas, beans, lentils, *etc.*), and other starch material sources and subsequent removal of glucose by yeast, followed by extensive purification of the resulting mixture of isomalto-oligosaccharides and formulation to produce a powder or syrup product. Several down-stream purification steps are employed in the manufacturing of Vitasugar™ to minimize the potential for the occurrence of any residues of the biocatalyst or other processing aids used during the production process in the final products.

Following oral consumption, the maltose-oligosaccharide fraction of the mixture, as well as the isomalto-disaccharides are largely hydrolyzed in the gastrointestinal tract to glucose, which is subsequently absorbed and utilized by the body in well characterized metabolic pathways. The remaining undigested isomalto-oligosaccharides traverse the gastrointestinal tract and are subjected to bacterial fermentation in the colon.

The results of the animal toxicity and human tolerance studies provide sufficient support that consumption of Vitasugar™, would not be expected to be associated with any adverse effects. In light of the lack of systemic absorption of the larger oligosaccharide components of IMO mixtures and absorption of only glucose from the hydrolysis of the smaller saccharides, the expected absence of any adverse effects related to IMO products was confirmed by several toxicity studies in which rats were administered mixtures of isomalto-oligosaccharides in the diet at concentrations of up to 20% for 5 to 6 weeks (Kaneko *et al.*, 1992; Day and Chung, 2004) or 3% in the drinking water for 1 year (Kaneko *et al.*, 1990). Examined *in vitro*, in bacterial and mammalian cells, IMO mixtures did not induce any mutagenic or genotoxic effects with or without metabolic activation (Kaneko *et al.*, 1990). Although no studies were identified which specifically assessed the potential effect of IMO consumption on reproduction or development, considering the lack of systemic absorption of the larger isomalto-oligosaccharides which comprise Vitasugar™ and hydrolysis of the smaller saccharides to glucose, there is no reason to suspect any potential reproduction or development toxicity.

While no gastrointestinal discomforts were reported by study participants in a single-dose (up to 40 g) and a repeat-dose (up to 15 g for 21 days) human tolerance study, increases in the incidence or severity of various gastrointestinal symptoms (abdominal distension and spasm, tormina, borborgymi, flatulence) were observed in comparison to pre-treatment in a few other studies in which IMO products were provided for oral ingestion at dose levels in the range of 10 to 30 g for 7 to 28 days. In a group of elderly subjects with a history of chronic constipation, consumption of up to 24 g of an IMO mix for 30 days significantly increased the defecation frequency and stool weight, but was not accompanied by any reports of gastrointestinal discomforts. Notably, no changes in the severity of gastrointestinal disturbances were reported by subjects consuming daily 10 g of an IMO preparation for 7 days in comparison to a group consuming a placebo (Bouhnik *et al.*, 2004). Although it is apparent that some variability was observed in the occurrence of gastrointestinal disturbances following ingestion of IMO

preparations among different studies, such variations are expected in light of the compositional differences among the IMO mixtures. Importantly, in none of the studies were increases reported in either the incidence or severity of diarrhea. At the intake levels of Vitasugar™ resulting from the proposed use-levels (*i.e.*, 30 g/day), Vitasugar™ is expected to be well-tolerated.

The scientific evidence presented above indicates that Vitasugar™, a mixture of isomalto-oligosaccharides, would not produce adverse effects on human health under the intended conditions of use described herein. Following oral consumption, the di- and trisaccharides in the mixture are largely hydrolyzed in the gastrointestinal tract to glucose, which is subsequently absorbed and utilized by the body in well characterized metabolic pathways. The remaining undigested isomalto-oligosaccharides pass through the gastrointestinal tract and are subjected to bacterial fermentation in the colon. Consequently, as supported by the results of the published animal toxicity studies, as well as human tolerance studies, there is no risk of systemic toxicity related to the ingestion of isomalto-oligosaccharides. The data and information summarized in this report support the conclusion that Vitasugar™, meeting appropriate food grade specifications and manufactured and used in accordance with current good manufacturing practice, would be GRAS based on scientific procedures under the intended conditions of use.

Conclusion

We, the Expert Panel, have independently and collectively, critically evaluated the data and information summarized above and conclude that Vitasugar™, a mixture of isomalto-oligosaccharides, meeting appropriate food-grade specifications and produced in accordance with current good manufacturing practice, is Generally Recognized as Safe (GRAS) based on scientific procedures under the conditions of intended use in foods specified herein.

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Table 1-A Physical and Chemical Specifications for Vitasugar™ (IMO-syrup and IMO-powder)			
Specification Parameter	**Specification**		**Analytical Methods**
	Syrup	**Powder**	
Solubility (water) (%)	N/A	≥99	-
Dried solids (g/100 g)	≥75	N/A	-
Glucose (% dry basis)	≤5[1]	≤5[1]	HPLC analysis
Isomaltose + DP3 to DP9 (% dry basis)	≥90[1]	≥90[1]	HPLC analysis
Moisture (%)	N/A	≤4	AOAC Method 925.45 (AOAC, 2000)[2]
pH	4 to 6	N/A	-
Sulfated ash (g/100 g)	≤0.3	≤0.3	<281> Residue on Ignition (USP, 2005)[3]
Heavy Metals			
Lead (mg/kg)	≤0 5	≤0.5	<251> Lead (USP, 2005)[3]
Arsenic (mg/kg)	≤0 5	≤0.5	<211> Arsenic (USP, 2005)[3]

N/A = Not applicable; DP = Degree of polymerization; HPLC = High Performance Liquid Chromatography; AOAC = American Organization of Analytical Chemists, USP = U S. Pharmacopeia.

[1] Based upon dried solids.

[2] AOAC. 2000. Chapter 44. Sugars and Sugar Products. 44.1.03 AOAC Official method 925.45. Moisture in Sugar. A. Vacuum Drying. Official Methods of Analysis of the Association of Official Analytical Chemists (17th Ed.). Association of Official Analytical Chemists (AOAC); Arlington, Virginia. Vols. 1&2. (2002, Revision 1). pp.1-2.

[3] USP. 2005. Test Methods <211> Arsenic, <241> Lead, <281> Residue on Ignition. United States Pharmacopeia (28th Ed) & National Formulary (23rd Ed.). U.S. Pharmacopeia (USP) Convention Inc.; Rockville, Maryland. pp. 2297-2298, 2300-2301, and 2303

Table 1-B Microbiological Specifications for Vitasugar™ (IMO-syrup and IMO-powder)			
Specification Parameter	**Specification**		**Analytical Methods**
	Syrup	**Powder**	
Total Aerobic Plate Count (CFU/g)	Less than 10,000	Less than 10,000	MFHPB-18
Yeast	Less than 100	Less than 100	MFHPB-22
Escherichia coli (MPN/g)	Less than 10	Less than 10	MFLB-80 and MFLB-90
Salmonella (CFU/g)	Absent	Absent	MFHPB-20

CFU = Colony forming unit; MPN = Most-probable-number, MFHPB = Microbial Analysis of Food Health Protection Branch; MFLB = Microbiological Food Laboratory Procedure.

Table 2 Summary of the Individual Proposed Food-Uses, Use-Levels, and Amount per Serving of Vitasugar™ in the United States (U.S.)			
Food-Uses	**Serving Size (grams)[1]**	**Maximum Use-Level (%)**	**Vitasugar™ Amount per Serving (grams)**
Baked Goods and Baking Mixes	60	25	15
Beverages and Beverage Bases	240	5	12
Breakfast Cereals	50	20	10
Condiments and Relishes	23	20	5
Dairy Product Analogs	240	5	12
Mayonnaise and Mayonnaise-type Dressings	23	30	7
Salad Dressings	30	30	9
Frozen Dairy Desserts and Mixes	100	10	10
Gelatins, Puddings, and Fillings	100	15	15
Gravies and Sauces	70	20	14
Hard Candies	10	100	10
Jams and Jellies	15	75	11
Meal Replacement Bars and Mixes	40	25	10
Meat Products	50	5	2.5
Milk and Milk Products	110	5	5 5
Nut Products	30	10	3
Processed Fruits and Fruit Juices	140	5	7
Snack Foods	30	5	1 5
Soft Candy	35	40	14
Sugar Substitutes	4	100	4
Sweet Sauces, Toppings, and Syrups	30	50	15
Processed Vegetables and Vegetable Juices	100	15	15

[1] Based on the Reference Amounts Customarily Consumed (RACC) Per Eating Occasion (21 CFR §101.12) (U.S. FDA, 2007c).

Table 3 Composition of Isomalto-Oligosaccharide (IMO) Products[1] Tested in the Published Studies (in alphabetical order)

Test Mat.	DP1 (%)		DP2 (%)			DP3 (%)				DP4 (%)		DP5 (%)		DP6 (%)		Other (%)		Reference
	Glu	Fru	M	IsoM	O	P	M	IsoM	O	M	IsoM	M	IsoM	M	IsoM	IMO	Dex	
Vitasuger*	-	-	5-6	10-15	-	20-25		25-30	-	-	15	-	7-9	-	4-5	<10	-	-
IMO	20.9	0.5	15.4	12.0	-	29.1	3.9	2.6	-	3.2	9.9	-		-		-	2.5	Chen *et al.* (2001); Wang *et al.* (2001)
IMO	<0.2%		6.9			28.4	-	-	-	36.7		19.1		7.4		1.2[2]	-	Day and Chung (2004)
IMO-900P	-	-	38.0			25.2				23.7[3]						-	-	Kaneko *et al.* (1990)
IMO-900	-	-	52.5			25.4				15.2[3]						-	-	
IMO-900P®	-	-	-	34.4	-	12.2	-	14.7	-	-	16.2	-		-		10.6	-	Kaneko *et al.* (1992)
IMO-900®	3.8	-	4.5	22.8	13.1[4]	11.6	0.9	16.7	-	17.7		7.2		1.7[5]		-	-	Kaneko *et al.* (1995); Oku and Nakamura (2003)
IMO-2	0.4	-	2.1	64.3	22.3	4.7	-	5.7	-	0.5		-		-		-	-	Kaneko *et al.* (1995)
IMO-3	0.5	-	1.2	1.8	2.4	25.3	2.2	16.5	-	30.7		8.5		10.9[5]		-	-	
IMO-900®	1.8	-	5.1	48.8	3.7	6.9	-	16.9	1.6	15.2[3]						-	-	Kohmoto *et al.* (1988)
IMO-900®	4.1	-	10.5[6]	37.2	-	See DP3 IsoM	See DP2 M	26.8[7]	See DP3 IsoM	21.4[3]						-	-	Kohmoto *et al.* (1991)
IMO-900®	2.4	-	3.6	32.3	9.1[4]	12.3	-	14.8	-	15.5		6.9		3.3		-	-	Kohmoto *et al.* (1992)
^{13}C-IMO-900®	1.2	-	2.0	32.6	6.9	13.4	-	16.9	-	15.5		6.9		4.6		-	-	

Mat. = Material; DP = Degree of polymerization, Glu = Glucose, Fru = Fructose, M = Malto-; IsoM = Isomalto-; O = Other, P = Panose; IMO = Isomaltooligosaccharides, Dex. = Dextrin; IMO-2 = Disaccharide fraction from IMO; IMO-3 = Tri- and higher oligosaccharide fraction from IMO.

* Composition based on representative samples – Product specifications indicate glucose ≤5% and ≥90% isomaltose and DP3 to DP9.

[1] Expressed on a dry basis (%).

[2] DP7 and greater.

[3] DP4 and greater.

[4] Nigerose and kojibiose.

[5] DP6 and greater.

[6] Maltose and maltotriose combined.

[7] All tri-isomalto-oligosaccharides

Table 4	Summary of Oral Subchronic and Chronic Animal Toxicity Studies with Isomalto-oligosaccharide (IMO) Products			
Species (strain, sex, no./group)	**Duration**	**Concentrations (Dose levels)**	**Study-end Results[1]**	**Reference**
Rat (Sprague-Dawley; male; 8/group)	35 days	0 (corn starch) or 20% in diet (~0 and 20 g/kg bw/day, respectively)	↓ in FUE and TG; No Δ in body weight, body weight gain, food intake, cecal contents, and relative organ weights (stomach, small intestine, cecum, colon, liver, kidney, retroabdominal adipose tissue); No Δ in serum and liver total Ch and PL, and serum HDL-Ch and NEFA.	Kaneko *et al.* (1992)
Rat (Sprague-Dawley; male; 5-6/group)	42 days	0 (Purina rat chow), 5, 10, or 20% in diet (~0, 5, 10, and 20 g/kg bw/day, respectively)	↑ in weight of cecum at 10 and 20%; ↓ (dose-dependent) in abdominal fat gain (normalized for food intake); No Δ in food intake, body weight gain, and absolute heart, spleen, kidneys, lungs, and brown and white adipose tissue weight.	Day and Chung (2004)
Rat (Wistar; male; 8/group)	365 days (1 year)	0 or 3% in drinking water (~0 and 3-5 g/kg bw/day, respectively)	No Δ in body weight gain and body weights, AST, ALP, LDH, Cre, BUN (↓ 1st month), UA, total Ch, TG, WBC, and RBC; ↓ in serum Hb, Ht, and ALT; No gross or histopathological abnormalities ↑ in *Lactobacillus* count and *Bifidobacterium* frequency of occurrence; ↓ *Clostridium.*	Kaneko *et al.* (1990)

No Δ = No variations between test and control animals; ALP = alkaline phosphatase; ALT = Alanine aminotransferase; AST = aspartate aminotransferase; BUN = Blood urea nitrogen; Ch = Cholesterol; Cre = Creatinine; FUE = Food utilization efficiency; Hb = Hemoglobin; HDL-Ch = High-density lipoprotein cholesterol; Ht = Hematocrit; LDH = Lactate dehydrogenase; NEFA = Non-esterified fatty acids; PL = Phospholipids; RBC = Red blood cell count; TG = Triglycerides, UA = Uric acid; WBC = White blood cell count;
[1] Study-end results unless otherwise indicated; Results are provided for test animals relative to controls.

Table 5 Summary of Human Tolerance Studies Conducted with Isomalto-oligosaccharide (IMO) Products				
Study Population and Study Design	**Duration**	**Daily Dose Levels**	**Results**	**Reference**
9 healthy males (~26 years old) and 29 females (~23 years old)	Single dose	10, 20, or 40 g	No GI disturbances.	Oku and Nakamura (2003)
81 healthy males and 119 females (~30 years old) (8 ingested IMO mix); double-blind placebo-controlled study	7 day run-in and 7-day treatment period	0 (placebo) or 10 g/day (2 equal portions)	↑ (slight) in excess flatus, bloating, borborygmi, and abdominal pains (all mild symptoms) *vs.* run-in period; however, no Δ in any of the GI symptoms *vs.* placebo control; None of the subjects experienced diarrhea.	Bouhnik *et al.* (2004)
6 healthy males (26-48 years old)	10 days	20 g/day	None of the subjects experienced diarrhea; only transient increase in flatulence in 2/24 subjects.	Kohmoto *et al.* (1988)
18 older subjects (5 males and 13 females; 50-93 years old)	14 days			
20 healthy females and 11 males (22 subjects w/ history of constipation) (~27 – 30 years old)	21 days (total)[2]	10 or 15 g	No GI disturbances. ↑ Defecation frequency in constipated subjects w/ 15 g IMO mix *vs.* 1st week.	Kaneko *et al.* (1993)
8 male and 12 female hemodialysis patients (~64 years old)	14-day run-in and 28-day treatment period	30 g/day (2 equal portions)	↑ in severity of distension (10%)[1], tormina (10.5%), borborgymi (6.1%), spasms (4.5%), and in bowel movements; No Δ in diarrhea (5%) Clinical Chemistry ↑ in Hb, Ht, and HDL-Ch *vs.* run-in; ↓ in Tg, total Ch; No Δ in glucose, albumin, total protein, BUN, Cre, Ca^{2+}, P, and LDL-Ch.	Wang *et al.* (2001)
7 elderly males w/ history of constipation (~75 years old)	30-day run-in and 30-day treatment period	↑ from 8 to 24 g (1st 10 days)	↑ in defecation frequency and wet and dry fecal weight per day and stool sample; no reports of GI disturbances. Clinical Chemistry ↑ in Na^+; No Δ glucose, total protein, albumin, TG, Ch, HDL-Ch, Ca^{2+}, P, and K *vs.* run-in.	Chen *et al.* (2001)

No Δ = No change; BUN = Blood urea nitrogen; Ca^{2+} = Calcium; Cre = Creatinine; Ch = Cholesterol; GI = Gastrointestinal; Hb = Hemoglobin; HDL-Ch = High-density lipoprotein cholesterol; Ht = Hematocrit; LDL-Ch = Low density lipoprotein cholesterol; K = Potassium; Na^+ = Sodium; P = Phosphorus; TG = Triglycerides.

[1] Percent in parentheses indicates percent of patients experiencing GI symptoms.

[2] 1st week run-in period; 2nd and 3rd week IMO mix ingestion; 4th week break; 5th week IMO mix ingestion.

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FCC, 2003 Monographs Used	
Monograph	**Pages**
Calcium chloride	64-65
Carbon, activated	94-96
Enzyme preparation	146-151
Food starch, unmodified	183-184
Hydrochloric acid	218-221
Sodium chloride	407
Sodium hydroxide	416-417
Yeast, dried	508-510

ATTACHMENT 1

***CURRICULA VITAE* OF EXPERT PANEL MEMBERS**

Joseph Francis Borzelleca

Educational Background:

B.S. St. Joseph's University, Philadelphia, PA, Major: Biology, Chemistry.

M.S. School of Graduate Studies, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA, Major: Pharmacology, Physiology.

Ph.D. School of Graduate Studies, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA. Major: Pharmacology, Biochemistry.

Academic Appointments

Instructor-Associate: Department of Pharmacology, Medical College of Pennsylvania, 1956-1959.

Assistant Professor: Department of Pharmacology, Toxicology, Medical College of Virginia, 1959-62 and 1962-1967.

Professor: Department of Pharmacology, Toxicology, Medical College of Virginia, 1967-

Head: Division of Toxicology, Department of Pharmacology, Toxicology, Medical College of Virginia, 1972-1986.

Professor Emeritus: Pharmacology & Toxicology, Department of Pharmacology, Toxicology, Medical College of Virginia, July 1996 –

Professional Certification

Fellow, Academy of Toxicological Sciences

Professional Affiliations

Societies

Academy of Toxicological Sciences* **

American Association for the Advancement of Science

American Chemical Society

American College of Toxicology*

American Society of Pharmacology and Experimental Therapeutics**

(Environmental Pharmacology Committee; Liaison Committee, SOT; Toxicology Committee)

International Society of Regulatory Toxicology and Pharmacology*

(Member of Council)

Sigma XI

Society of Experimental Biology and Medicine*

(Councilor; Program Chairman of Southeastern Section)

Society for Risk Analysis

Society of Toxicology* **
(Member and/or Chairman: Awards, Education, Legislative Affairs, Membership, Nominating Committees; Secretary of the Society, Councilor, and President; President, Food Safety Specialty Section)

Virginia Academy of Science*

(Chairman, Medical Sciences Division)

* Held elected office
** Held appointed office or position

Board of Directors

ILSI

Board of Scientific and Policy Advisors

American Council on Science and Health

Journals

Editor, Food Chemical Toxicology, 1992-

Editorial Board

Environmental Carcinogenesis Reviews, 1981-

Journal of Environmental Pathology, Toxicology and Oncology 1977-

Journal of Environmental Science and Health, 1979-

Journal of the American College of Toxicology, 1982-

Journal of Toxicology: Cutaneous and Ocular Toxicology, 1982- 1992

Journal of Applied Toxicology, 1989-

Pharmacology, 1978-

Pharmacology and Drug Development, 1980-

Toxicology and Applied Pharmacology, 1975-1978

Consultantships (Past, Present)

Governmental

- Food and Drug Administration
- National Institute of Mental Health
- National Cancer Institute
- Environmental Protection Agency
- Department of Labor - OSHA (Chairman, Carcinogens Standards Committee)
- U.S. Army - Research and Development Command

Non-Governmental

- National Academy of Sciences - NRC
  - Committee on Toxicology (Member, Chairman)/Board on Toxicology and Environmental Health Hazards
  - Safe Drinking Water Committee
  - Evaluation of Household Substances Committee (1138 Committee)
  - Food Protection Committee
  - Food Additives Survey Committee
  - Committee on Risk-Based Criteria for Non-RCRA Hazardous Wastes
  - Committee on Risk Assessment of Flame-Retardant Chemicals
- Federation of American Societies of Experimental Biology
  - Select Committee on GRAS Substances
  - Flavors and Extracts
  - Biotechnology Product Safety
  - Caprenin GRAS Committee
- World Health Organization
  - Joint Meeting on Pesticide Residues (JMPR) (Member, Chairman)
- NATO/CCMS Drinking Water Committee

Industrial

- Chemical Companies; Trade Associations

University Activities

Related to Instruction

Prepared a laboratory manual in pharmacology (animal and human studies) (1960)
Introduced the use of closed circuit TV and TV tapes in pharmacology (11960)
Introduced clinical pharmacological experiments into the medical and dental programs (1960)

Planning and participation in continuing education program
(Schools of Dentistry, Medicine and Pharmacy)

Planning and administering each of the three major efforts in pharmacology

(dental, medical, pharmacy) since 1960.

Graduate Program - assisted in developing graduate training program in toxicology

Current Teaching Activities

Presents lectures on Toxicological Issues, Food Intake and Control

Not Directly Related to Instruction

Elected senator from the graduate school, then vice-president of the University Senate
Served on various committees (e.g. Curriculum, Search, Animal Care) in each of the four major schools (Dentistry, Graduate, Medical, Pharmacy)

Research

Research was continuously funded from 1956. Sources of support included governmental (U.S.P.H.S.; N.I.H; E.P.A.; N.I.D.A.) and non-governmental (industrial). A list of publications is attached).

Awards

DOD - US Army - Chemical Research Development and Engineering Center

Distinguished Service Award, 1986

National Italian - American Foundation Award

Excellence in Medicine and Community Service, 1987

Thomas Jefferson University

Distinguished Alumnus Award, 1987

Virginia Commonwealth University - School of Basic Health Sciences

Outstanding Faculty Award, 1987

Virginia Commonwealth University - School of Basic Health Sciences, Dept. of Pharmacology and Toxicology

Professor of the Year- 1992

American College of Toxicology

Distinguished Service Award- 1997

Virginia's Life Achievement in Science Award- April 2001

2001 Bernard L. Oser Food Ingredient Safety Award by the Institute of Food Technologists

PUBLICATIONS

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Borzelleca, J.F.: The absorption of nicotine from the urinary bladder of the dog. Arch. Int. Pharmacodyn. 133:444, 1961.

Borzelleca, J.F., Bowman, E.R. and McKennis, H., Jr.: The cardiovascular and respiratory effects of (-)-cotinine. J. Pharmacol. Exp. Ther. 137:313,1962.

Borzelleca, J.F.: Drug absorption from the urinary tract of the rat. Nicotine. Arch. Int. Pharmacodyn. 143:595,1963.

Borzelleca, J.F.: Influence of saline and glucose infusions on the course of barbiturate intoxication. Arch. Int. Pharmacodyn. 146: 163, 1963.

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Borzelleca, J.F.: Drug movement from the isolated urinary bladder of the rabbit. Arch. Int. Pharmacodyn.154:40,1965.

Borzelleca, J.F.: Rabbit urinary bladder potentials. Invest. Urol. 3: 77, 1965.

Borzelleca, J.F.: Studies on the mechanisms of drug movement from the isolated urinary bladder. J. Pharmacol. Exp. Ther. 148: 111, 1965.

Lowenthal, W. and Borzelleca, J.F.: Drug absorption from the rectum. I. J. Pharm. Sci. 54:1790, 1965.

Ambrose, A.M., BorzelleGa, J.F., Larson, P.S., Smith, R.B., Jr. and Hennigar, G.R.: Toxicologic studies on monochloroacetaldehyde: 2,4-dinitrophenylhydrazone, a foliar fungicide. Toxicol. Appl. Pharmacol. 8:472, 1966.

Borzelleca, J.F. and Doyle, C.H.: Excretion of drugs in saliva. Salicylate, barbiturate, sulfanilamide. J. Oral. Therap. Pharmacol. 3:104, 1966.

Borzelleca, J.F. and Lowenthal, W.: Drug absorption from the rectum. II. J. Pharm. Sci. 55:151, 1966.

Wooles, W.R. and Borzelleca, J.F.: Prolongation of barbiturate sleeping time in mice by stimulation of the reticuloendothelial system. J. Reticuloendo. Soc. 3:41, 1966.

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Borzelleca, J.F., Harris, T. and Bernstein, S.: The effect of DIVISO on drug movement through the wall of the urinary bladder of the rabbit. J. Invest. Urol. 6:43, 1968.

Borzelleca, J.F.: The excretion of glucose in saliva. Dog. J. Oral Therap. Pharmacol. 4:338, 1968.

Kim, K.S., Borzelleca, J.F., McKennis, H. and Bowman, E.R.: Pharmacological effects of some nicotine metabolites and related compounds. J. Pharmacol. Exp. Ther. 161:59, 1968.

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BorzelleGa, J.F. and Putney, J.W., Jr.: A model for the movement of salicylate across the parotid epithelium. J. Pharmacol. Exp. Ther. 174:527, 1970.

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Lowenthal, W., BorzelleGa, J.F. and Corder, C.D., Jr.: Drug absorption from the rectum. 111. Aspirin and some aspirin derivatives. J. Pharm. Sci. 59: 1353, 1970.

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Egle, J.L., Jr., Guzelian, P.S. and Borzelleca, J.F.: Time course of the acute toxic effects of sublethal doses of chlordecone (Kepone). Toxicol. Appl. Pharmacol. 48:533, 1979.

Larson, P.S., Egle, J.L., Jr., Hennigar, G.R. and Borzelleca, J.F.: Acute and subchronic toxicity of mirex in the rat, dog, and rabbit. Toxicol. Appl. Pharmacol. 49:271, 1979.

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Simon, G.S., Tardiff, R.G. and Borzelleca, J.F.: Failure of hexachlorobenzene to induce dominant lethal mutations in the rat. Toxicol. Appl. Pharmacol. 47:415, 1979.

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Carmines, E.L., Carchman, R.A. and Borzelleca, J.F.: A method for the evaluation of dose-effect data utilizing a programmable calculator. J. Environ. Path. and Tox. 4:23, 1980.

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Skalsky, H.L., Wrenn, J.M. and Borzelleca, J.F.: *In vitro* and *in vivo* evaluation of the movement of Kepone in the rat submaxillary gland. J. Environ. Path. and Tox. 3:529, 1980.

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Smith, L.W. and Borzelleca, J.F.: *In vitro* stimulation of oxygen consumption in rat submaxillary gland by pilocarpine. J. Dent. Res. (59)9:1539, 1980.

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Smith, L.W. and Borzelleca, J.F.: Movement of mercury in rat submaxillary slices. Toxicology 18:169, 1980.

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Carmines, E.L., Carchman, R.A. and BorzelleGa, J.F.: Investigations into the mechanism of paraquat toxicity utilizing a cell culture system. Toxicol. Appl. Pharmacol. 58:353, 1981.

Simon, G.S., Borzelleca, J.F. and Dewey, W.L.: Narcotics and diabetes 11. Streptozotocin-induced diabetes selectively alters the potency of certain narcotic analgesics. Mechanism of diabetes: morphine interaction. J. Pharmacol. Exp. Ther. 218:324, 1981.

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Evaluation of the health aspects of butylated hydroxytoluene as a food ingredient. 1973.

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Evaluation of the health aspect of pulps as they may migrate to food from packaging materials. 1973.

Evaluation of the health aspects of propylene glycol and propylene glycol monostearate as food ingredients. 1973.

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Evaluation of the health aspects of agar-agar as a food ingredient. 1973.

Evaluation of the health aspects of certain red and brown algae as food ingredients. 1973.

Evaluation of the health aspects of cellulose and certain cellulose derivatives of food ingredients. 1973.

Iodine in foods: chemical methodology and sources of iodine in the human diet. 1974.

Evaluation of the health aspects of aconitic acid as a food ingredient. 1974.

Evaluation of the health aspects of stannous chloride as a food ingredient. 1974.

Evaluation of the health aspects of licorice, glycyrrhiza and ammoniated glycrrhizin as food ingredients. 1974.

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Evaluation of the health aspects of sorbose as a food ingredient. 1974.

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Evaluation of the health aspects of potassium iodide, potassium iodate, and calcium iodate as food ingredients. 1975.

Evaluation of the health aspects of dextran as food ingredients. 1975.

Evaluation of the health aspects of calcium oxide and calcium hydroxide as food ingredients. 1975.

Evaluation of the health aspects of succinic acid as a food ingredient. 1975.

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of certain calcium salts as food ingredients. 1975.

Evaluation of the health aspects of glycerin and glycerides as food ingredients 1975

Evaluation of the health aspects of dextrin and corn dextrin as food ingredients. 1975.

Evaluation of the health aspects of sodium thiosulfate as a food ingredient. 1975.

Evaluation of the health aspects of gelatin as a food ingredient. 1975.

Evaluation of the health aspects of bile salts and ox bile extract as food ingredients. 1975.

Evaluation of the health aspects of choline chloride and choline bitartrate as food ingredients. 1975.

Evaluation of the health aspects of aluminum compounds as food ingredients. 1975.

Evaluation of the health aspects of tallow, hydrogenated tallow, stearic acid, and calcium stearate as food ingredients. 1975.

Evaluation of the health aspects of phosphates as food ingredients. 1975.

Evaluation of the health aspects of the tocopherols and a-tocopheryl acetate as food ingredients. 1975.

Evaluation of the health aspects of sorbic acid and its salts as food ingredients. 1975.

Evaluation of the health aspects of hydrogenated fish oil as a food ingredient. 1975.

Evaluation of the health aspects of beeswax (yellow or white) as a food ingredient. 1975.

Evaluation of the health aspects of inositol as a food ingredient. 1975.

Evaluation of the health aspects of malic acid as a food ingredient. 1975.

Evaluation of the health aspects of Japan Wax as a substance migrating to food from cotton or cotton fabrics used in dry food packaging. 1976.

Evaluation of the health aspects of carnauba wax as a food ingredient. 1976.

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Evaluation of the health aspects of gum guaiac as a food ingredient. 1976.

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Evaluation of the health aspects of tall oil as it may migrate to foods from packaging materials. 1976

Evaluation of the health aspects of corn sugar (dextrose), corn syrup and invert sugar as food ingredients. 1976.

Evaluation of the health aspects of sucrose as a food ingredient. 1976.

Evaluation of the health aspects of sulfiting agents as food ingredients. 1976.

Evaluation of the health aspects of glycerophosphates as food ingredients. 1976.

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Evaluation of the health aspects of pectin and pectinates as food ingredients. 1977.

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Evaluation of the health aspects of rennet as a food ingredient. 1977.

Evaluation of the health aspects of acetic acid and sodium acetate as food ingredients. 1977.

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Evaluation of the health aspects of casein, sodium Gaseinate, and calcium caseinate as food ingredients. 1979.

Evaluation of the health aspects of nickel as a food ingredient. 1979

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Evaluation of the health aspects of manganous salts as food ingredients. 1979.

Evaluation of the health aspects of copper gluconate, copper sulfate, and cuprous iodide as food ingredients. 1979.

Evaluation of the health aspects of hydrochloric acid as a food ingredient. 1979.

Evaluation of the health aspects of lecithin as a food ingredient. 1979.

Evaluation of the health aspects of potassium acid tartrate, sodium potassium tartrate, sodium tartrate and tartaric acid as food ingredients. 1979.

Evaluation of the health aspects of starter distillate and diacetyl as food ingredients. 1980.

Vitamin A, Vitamin A Acetate, and Vitamin A Palmitate as food ingredients. 1980.

Evaluation of the health aspects of iron and iron salts as food ingredients. 1980.

Evaluation of the health aspects of protein hydrolyzates as food ingredients. 1980.

Evaluation of the health aspects of collagen as a food ingredient. 1981.

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Evaluation of the health aspects of soya fatty acid amines as food ingredients. 1981.

Evaluation of the health aspects of activated carbon (charcoal) as a food processing aid. 1981.

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Evaluation of the health aspects of corn mint oil as a food ingredient. 1981.

Evaluation of the health aspects of a mixture. Evaluation of the health aspects of diferrous, dipotassium ferrous, and potassium ferrocyanides as finding agents in wine production. 1981.

Evaluation of the health aspects of wheat gluten, corn gluten, and zein as food ingredients. 1981.

Evaluation of the health aspects of peptones as food ingredients. 1981.

Evaluation of the health aspects of shellac and shellac wax as food ingredients. 1981.

Evaluation of the health aspects of sodium metasilicate and sodium zinc metasilicate as food ingredients. 1981.

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Central States Regional Chapter, 1986-
Program Committee (Chairman), 1985-1986
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Awards Committee (Chairman), 1987-1988
Nominating Committee (Chairman), 1988-1989
Council Member, 1981-1988
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American Academy of Clinical Toxicology, 1970-1996
Board of Trustees, 1972-1977
Canadian Academy of Clinical Toxicology, 1976-1989
Program Committee, 1976-1977
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American Board of Toxicology, 1979-1983
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President, 1982-1983
American Water Works Association, 1983-1995
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Committee on Mixtures (Chairman), 1986-1988
Committee on Toxicology (Chairman), 1987-1993
Committee on Risk Assessment of Hazardous Air Pollutants, 1990-1993
Committee to Study the Interactions of Drugs, Biologics and Chemicals in Deployed U. S. Military Forces, 1995-1996
Subcommittee on Acute Exposure Guideline Levels, 1997-2003
Board on on Environmental Studies and Toxicology (Vice Chair)1999-2003
Committee on the Use of Third Party Toxicity Research with Human Participants, Science Technology and Law Program, 2002-2004
Subcommittee on Fluoride in Drinking Water (chair) 2003-
Environmental Protection Agency, Washington, D.C., 1976-1995
FIFRA Science Advisory Panel, 1976-1980
Worker Re-entry Protocol Group, 1977-1978
Committee on Tolerances, 1978-1979
Science Advisory Board, Environmental Health Committee, 1980-1989
Organics Subcommittee (Chairman), 1986-1989
Estimating Risks from Dioxins/Dibenzofurans, 1986-1987
Severity of Effects Ranking Schemes, 1985-1986
Acute Toxics Committee, 1986-1987
Hazard Ranking System Committee, 1987-1988
Dioxin Reassessment Review Committee 1995
Science Advisory Board, Environmental Health Committee, 1997-2001
National Institute of Environmental Health Sciences, 1975-1978
NIEHS Advisory Council, 1975-1978
University-Based Centers Subcommittee (Chairman), 1975-1978
Second Task Force on Human Health and the Environment, 1976-1977
Biologic Mechanisms and Toxicity Subcommittee, 1976-1977
F.E.M.A., Washington, D.C., Expert Panel Member, 1977-2003
National Advisory Committee, California Primate Center, Davis, 1977-1980

OTA, Wash., Panel on Assessment of Environmental Contaminants, 1978
National Toxicology Program, Board of Scientific Counselors Ad Hoc Panel on Chemical Carcinogenesis Testing & Evaluation, 1982-1984
DHHS Advisory Committee on Long-term Health Effects of Phenoxy Herbicides and Contaminants, 1982-1985
UAREP Panel on Health Aspects of Waste Chemical Disposal, 1983-1984
Nutrition Foundation, Washington Committee, 1982-1983, DC
Predictive Role of Mouse Liver Tumors
National Sanitation Foundation, Ann Arbor, 1983-1989
Council of Public Health Consultants, 1983-1989
Health Advisory Board, 1983-1989
Drinking Water Additives Peer Review Group, 1987-1989
Kansas Dept. Health and Environment, Topeka, 1983-1987
Toxicology Advisory Committee, 1983-1987
Governors Advisory Committee on Radon (Chairman), 1987-1988
Governors Surface Water Quality Commission 1997-1999
National Institute of Occupational Safety and Health, 1984-1987
Board of Scientific Counselors, 1984-1987
White House Advisory Panel on Ranchhand Veterans, 1984-1986
Clean Sites Inc., Alexandria, Technical Advisory Panel, 1984-1993
Naylor Dana Institute, Advisory Panel on Acetaminophen, 1986-1987
Denver Water Dept. Reuse Demo. Project Advisory Committee, 1986-1992
Scientific Advisory Panel on Ground Water Recharge (California), 1987
Water Resource Recovery Pilot Plant Project (Tampa, FL), 1987-1992
Health Effects Group (Chairman), 1987-1992
International Life Sciences Institute, Risk Science Institute, 1988-
Armed Forces Epidemiological Board, 1988-1991
Lovelace Biomedical & Environmental Res. Inst. Board of Directors, 1988
Presidential Risk Assessment & Management Commission, 1990-1998
Food and Drug Administration, CFSAN Review Panel 1999
Food and Drug Administration, OPS Advisory Committee, 1999-2002
FDA, OPS Adv Com: Non-clinical studies subcommittee (chair), 1999-2003

LOCAL COMMITTEES:

Poison Control Center Committee (Chairman), 1968-1980
Pharmacy and Therapy Committee (Chairman), 1969-1984
Basic Science Lectureship Committee, 1970-1972
Health Care Delivery Systems Committee, 1971-1972

Research Committee, 1971-1973
Animal Care Committee, 1972-1974
Computer Committee (Chairman), 1972-1974
Search Committee for Chair of Biochemistry, 1975
Search Committee for Dean of School of Nursing (Chairman), 1975
Education Committee, 1976-1977
Faculty Promotion and Tenure Committee, 1976-1977
Curriculum Implementation Committee, 1976
Ad Hoc Ethics Committee, 1976
Long Range Planning Committee, 1976
Information Systems Advisory Committee, 1977
Medical Center Safety Committee (Chairman), 1978-1983
Radiation Safety Committee, 1978-1983
Biohazards Committee, 1978-1983
Engineering Safety Committee, 1978-1983
Committee for Intercampus Liaison (Chairman), 1978-1980
Search Committee for Director of Biomed. Engineering (Chairman), 1980
Search Committee for Graduate School Dean (Chairman), 1980
Task Force on Need for School of Public Health, 1980
Education and Curriculum Committee, 1984-1987
Center for Environmental and Occupational Health (Director 1986-1989)
Executive Advisory Committee, 1986-1989
External Advisory Committee, 1986-1989

HONORS/AWARDS:

Sigma Xi (Univ. of Chicago), 1960
Alpha Omega Alpha (Univ. of Kansas), 1973
The Kenneth P. DuBois Award (Midwest Chapter SOT), 1985
Samuel Kuna Award (Rutgers Univ.), 1989
Commander's Award for Public Service (Armed Forces Epidemiological Board), 1990
International Achievement Award (International Society of Regulatory Toxicology), 1990
Ambassador of Toxicology Award (Mid-Atlantic Chapter Society of Toxicology), 1991
Distinguished Medical Alumnus Award (Univ. of Chicago), 1991
Stokinger Award (Amer. Cont. Governmental Industrial Hygienists), 1992
John Doull Award (Mid-America Chapter Society of Toxicology), 1992

Special Recognition Award (University of Kansas Medical Center), 1992
Merit Award (Society of Toxicology), 1993
Snider Award (University of Arkansas Toxicology Symposium Series), 1994
Founders Award (Chemical Industry Institute of Toxicology), 1996
Distinguished Service Award, (American College of Toxicology), 1996
The Meritorious Service Award (Amer. Conf. Gov. Ind. Hygienists), 1996
Honorary Doctor of Pharmacy (The University of Kuopio, Finland), 1996

BOOKS/BOOK CHAPTERS:

Essays in Toxicology (F. Blood, ed.), Academic Press, New York, Effect of Physical Environmental Factors on Drug Response, 1972.

Casarett and Doull's Toxicology: The Basic Science of Poisons, Macmillan Publishing Co., Inc., New York.
First Edition (L. J. Casarett and J. Doull, eds.), 1975
Second Edition (C. D. Klaassen, M. O. Amdur and J. Doull, eds.), 1980
Third Edition (C. D. Klaassen, M. O. Amdur and J. Doull, eds.), 1986
Fourth Edition (M. O. Amdur, J. Doull and C. D. Klaassen, eds.), 1991
Fifth Edition (C. D. Klaassen ed., M. O. Amdur and J. Doull, emeritus eds.) 1995

Insecticide Biochemistry and Physiology (C. Wilkinson, ed.), Plenum Press, NY, The Treatment of Insecticide Poisoning, 1976.

Information Technology in Health Science Education (E. Deland, ed.), Plenum Pub. Co., Use of CATS in Pharmacology, 1978.

Food Safety (H. Roberts, ed.), Wiley & Sons, New York, Chapter 7, Food Safety and Toxicology, 1981.

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Methods to Assess Adverse Effects of Pesticides on Non-target Organism (R. G. Tardiff, ed.), John Wiley & Sons Ltd., Chapter 10, Assessment of Acute Toxicity of Pesticides on Humans and Domestic Animals, 1992.

Science and Judgement in Risk Assessment, Ed. Kurt Isselbacher, National Academy Press, Washington D. C. 1995

Environmental Toxicology, Current Developments (J. Rose Ed.), Chapter 1, General Principles of Toxicology, Gordon and Breach, Amsterdam , 1998

Acute Exposure Guideline Levels for Selected Airborne Chemicals, National Academy Press, Washington, D.C., 2000, 2001, 2002, 2003

Handbook of Pesticide Toxicology, Associate Editor, R. Krieger Ed., Vol 1. Principles, Vol 2. Agents, Academic Press, San Diego, 2000
Vol 1, Chapter 1, Dose Time and Other Factors Influencing Toxicity.

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St. Anselm's College, New Hampshire	B.A.	1964	Biology
University of New Hampshire, Durham, NH	M.S.	1967	Zoology
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RESEARCH AND PROFESSIONAL EXPERIENCE:

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1973-77 Lecturer, Northeastern University of Boston, MA
1973-78 Research Associate in Nutrition, Harvard School of Public Health, Boston, MA
1977-85 Lecturer in Nutrition, Harvard School of Public Health, Boston, MA
1978-82 Assistant Professor of Comparative Pathology, Harvard Medical School, New England Regional Primate Research Center, Southborough, MA
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1994- Director, Center for Health & Disease Research, University of Massachusetts-Lowell, Lowell, MA
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Publications:

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